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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:		(11) International Publication Number: WO 99/31236
C12N 15/12, C07K 14/47, 16/18, C120 1/68	A2	(43) International Publication Date: 24 June 1999 (24.06.99)
1/68         International Application Number: PCT/IB98         International Filing Date:       17 December 1998 (17)         Priority Data:       60/069,957       17 December 1997 (17.12.97)         60/074,121       9 February 1998 (09.02.98)         60/081,563       13 April 1998 (13.04.98)         60/096,116       10 August 1998 (10.08.98)	.12.97) [1.98] [	BY, CA, CH, CN, CU, CZ, DE, DK, EF, ES, FI, GB, GE GII, GM, IIR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW) Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM) European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN TD, TG).  Published  Without international search report and to be republished upon receipt of that report.

#### (57) Abstract

The sequences of extended cDNAs encoding secreted proteins are disclosed. The extended cDNAs can be used to express secreted proteins or portions thereof or to obtain antibodies capable of specifically binding to the secreted proteins. The extended cDNAs may also be used in diagnostic, forensic, gene therapy, and chromosome mapping procedures. The extended cDNAs may also be used to design expression vectors and secretion vectors.

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#### EXTENDED cDNAS for secreted proteins

The present application relates to extended cONAs which were disclosed in several United States Provisional Patent Applications. Table I lists the SEQ IO Nos. of the extended cONAs in the present application, the SEQ IO Nos. of the identical or nearly identical extended cONAs in the provisional applications, and the identities of the provisional applications in which the extended cONAs were disclosed.

#### Background of the Invention

The estimated 50,000-100,000 genes scattered along the human chromosomes offer tremendous promise for the understanding, diagnosis, and treatment of human diseases. In addition, probes capable of specifically hybridizing to loci distributed throughout the human genome find applications in the construction of high resolution chromosome maps and in the identification of individuals.

In the past, the characterization of even a single human gene was a painstaking process, requiring years of effort. Recent developments in the areas of cloning vectors, DNA sequencing, and computer technology have merged to greatly accelerate the rate at which human genes can be isolated, sequenced, mapped, and characterized. Cloning vectors such as yeast artificial chromosomes (YACs) and bacterial artificial chromosomes (BACs) are able to accept DNA inserts ranging from 300 to 1000 kilobases (kb) or 100-400 kb in length respectively, thereby facilitating the manipulation and ordering of DNA sequences distributed over great distances on the human chromosomes. Automated DNA sequencing machines permit the rapid sequencing of human genes. Bioinformatics software enables the comparison of nucleic acid and protein sequences, thereby assisting in the characterization of human gene products.

Currently, two different approaches are being pursued for identifying and characterizing the genes distributed

20 along the human genome. In one approach, large fragments of genomic DNA are isolated, cloned, and sequenced.

Potential open reading frames in these genomic sequences are identified using bio-informatics software. However, this approach entails sequencing large stretches of human DNA which do not encode proteins in order to find the protein encoding sequences scattered throughout the genome. In addition to requiring extensive sequencing, the bio-informatics software may mischaracterize the genomic sequences obtained. Thus, the software may produce-false positives in which non-coding DNA is mischaracterized as coding DNA or false negatives in which coding DNA is mischaracterized as non-coding DNA.

An alternative approach takes a more direct route to identifying and characterizing human genes. In this approach, complementary DNAs (cDNAs) are synthesized from isolated messenger RNAs (mRNAs) which encode human proteins. Using this approach, sequencing is only performed on DNA which is derived from protein coding portions of the genome. Often, only short stretches of the cDNAs are sequenced to obtain sequences called expressed sequence tags (ESTs). The ESTs may then be used to isolate or purify extended cDNAs which include sequences adjacent to the EST sequences. The extended cDNAs may contain all of the sequence of the EST which was used to obtain them or only a portion of the sequence of the EST which was used to obtain them. In addition, the extended cDNAs may contain the full coding sequence of the gene from which the EST was derived or, alternatively, the extended cDNAs may include

portions of the coding sequence of the gene from which the EST was derived. It will be appreciated that there may be several extended cDNAs which include the EST sequence as a result of alternate splicing or the activity of alternative promoters.

In the past, the short EST sequences which could be used to isolate or purify extended cDNAs were often 5 obtained from oligo-dT primed cDNA libraries. Accordingly, they mainly corresponded to the 3' untranslated region of the mRNA. In part, the prevalence of EST sequences derived from the 3' end of the mRNA is a result of the fact that typical techniques for obtaining cDNAs, are not well suited for isolating cDNA sequences derived from the 5' ends of mRNAs. (Adams et al., *Nature* **377**:174, 1996, Hillier et al., *Genome Res.* **6**:807-828, 1996).

In addition, in those reported instances where longer cDNA sequences have been obtained, the reported 10 sequences typically correspond to coding sequences and do not include the full 5' untranslated region of the mRNA from which the cDNA is derived. Such incomplete sequences may not include the first exon of the mRNA, particularly in situations where the first exon is short. Furthermore, they may not include some exons, often short ones, which are located upstream of splicing sites. Thus, there is a need to obtain sequences derived from the 5' ends of mRNAs which can be used to obtain extended cDNAs which may include the 5' sequences contained in the 5' ESTs.

While many sequences derived from human chromosomes have practical applications, approaches based on the identification and characterization of those chromosomal sequences which encode a protein product are particularly relevant to diagnostic and therapeutic uses. Of the 50,000-100,000 protein coding genes, those genes encoding proteins which are secreted from the cell in which they are synthesized, as well as the secreted proteins themselves, are particularly valuable as potential therapeutic agents. Such proteins are often involved in cell to cell communication and 20 may be responsible for producing a clinically relevant response in their target cells.

In fact, several secretory proteins, including tissue plasminogen activator, G-CSF, GM-CSF, erythropoietin, human growth hormone, insulin, interferon- $\alpha$ , interferon- $\beta$ , interferon- $\gamma$ , and interleukin-2, are currently in clinical use. These proteins are used to treat a wide range of conditions, including acute myocardial infarction, acute ischemic stroke, anemia, diabetes, growth hormone deficiency, hepatitis, kidney carcinoma, chemotherapy induced neutropenia and 25 multiple sclerosis. For these reasons, extended cDNAs encoding secreted proteins or portions thereof represent a particularly valuable source of therapeutic agents. Thus, there is a need for the identification and characterization of secreted proteins and the nucleic acids encoding them.

In addition to being therapeutically useful themselves, secretory proteins include short peptides, called signal peptides, at their amino termini which direct their secretion. These signal peptides are encoded by the signal sequences 30 located at the 5' ends of the coding sequences of genes encoding secreted proteins. Because these signal peptides will direct the extracellular secretion of any protein to which they are operably linked, the signal sequences may be exploited to direct the efficient secretion of any protein by operably linking the signal sequences to a gene encoding the protein for which secretion is desired. This may prove beneficial in gene therapy strategies in which it is desired to deliver a particular gene product to cells other than the cell in which it is produced. Signal sequences encoding signal peptides

also find application in simplifying protein purification techniques. In such applications, the extracellular secretion of the desired protein greatly facilitates purification by reducing the number of undesired proteins from which the desired protein must be selected. Thus, there exists a need to identify and characterize the 5' portions of the genes for secretory proteins which encode signal peptides.

Public information on the number of human genes for which the promoters and upstream regulatory regions have been identified and characterized is quite limited. In part, this may be due to the difficulty of isolating such regulatory sequences. Upstream regulatory sequences such as transcription factor binding sites are typically too short to be utilized as probes for isolating promoters from human genomic libraries. Recently, some approaches have been developed to isolate human promoters. One of them consists of making a CpG island library (Cross, S.H. et al., 10 Purification of CpG Islands using a Methylated DNA Binding Column, Nature Genetics 6: 236-244 (1994)). The second consists of isolating human genomic DNA sequences containing Spel binding sites by the use of Spel binding protein. (Mortlock et al., Genome Res. 6:327-335, 1996). Both of these approaches have their limits due to a lack of specificity or of comprehensiveness.

5' ESTs and extended cDNAs obtainable therefrom may be used to efficiently identify and isolate upstream 15 regulatory regions which control the location, developmental stage, rate, and quantity of protein synthesis, as well as the stability of the mRNA. (Theil et al., BioFactors 4:87-93, (1993). Once identified and characterized, these regulatory regions may be utilized in gene therapy or protein purification schemes to obtain the desired amount and locations of protein synthesis or to inhibit, reduce, or prevent the synthesis of undesirable gene products.

In addition, ESTs containing the 5' ends of secretory protein genes or extended cDNAs which include 20 sequences adjacent to the sequences of the ESTs may include sequences useful as probes for chromosome mapping and the identification of individuals. Thus, there is a need to identify and characterize the sequences upstream of the  $5^{\prime}$ coding sequences of genes encoding secretory proteins.

#### Summary of the Invention

The present invention relates to purified, isolated, or recombinant extended cDNAs which encode secreted 25 proteins or fragments thereof. Preferably, the purified, isolated or recombinant cDNAs contain the entire open reading frame of their corresponding mRNAs, including a start codon and a stop codon. For example, the extended cDNAs may include nucleic acids encoding the signal peptide as well as the mature protein. Alternatively, the extended cDNAs may contain a fragment of the open reading frame. In some embodiments, the fragment may encode only the sequence of the mature protein. Alternatively, the fragment may encode only a portion of the mature protein. A further aspect of the 30 present invention is a nucleic acid which encodes the signal peptide of a secreted protein.

The present extended cDNAs were obtained using ESTs which include sequences derived from the authentic 5' ends of their corresponding mRNAs. As used herein the terms "EST" or "5' EST" refer to the short cDNAs which were used to obtain the extended cDNAs of the present invention. As used herein, the term "extended cDNA" refers to the cDNAs which include sequences adjacent to the 5' EST used to obtain them. The extended cDNAs may contain all or a

portion of the sequence of the EST which was used to obtain them. The term "corresponding mRNA" refers to the mRNA which was the template for the cDNA synthesis which produced the 5' EST. As used herein, the term "purified" does not require absolute purity; rather, it is intended as a relative definition. Individual extended cDNA clones isolated from a cDNA library have been conventionally purified to electrophoretic homogeneity. The sequences obtained from these clones could not be obtained directly either from the library or from total human DNA. The extended cDNA clones are not naturally occurring as such, but rather are obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The conversion of mRNA into a cDNA library involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection. Thus, creating a cDNA library from messenger RNA and subsequently isolating individual clones from that library results in an approximately 10<sup>4</sup>-10<sup>6</sup> fold purification of the native message. Purification of starting material or natural material to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

As used herein, the term "isolated" requires that the material be removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide present in a living animal is not isolated, but the same polynucleotide, separated from some or all of the coexisting materials in the natural system, is isolated.

As used herein, the term "recombinant" means that the extended cDNA is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. Additionally, to be "enriched" the extended cDNAs will represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. Backbone molecules according to the present invention include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Preferably, the enriched extended cDNAs represent 15% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. More preferably, the enriched extended cDNAs represent 50% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. In a highly preferred embodiment, the enriched extended cDNAs represent 90% or more of the number of nucleic acid inserts in the population of recombinant backbone molecules. "Stringent", "moderate," and "low" hybridization conditions are as defined in Example 29.

Unless otherwise indicated, a "complementary" sequence is fully complementary. Thus, extended cDNAs encoding secreted polypeptides or fragments thereof which are present in cDNA libraries in which one or more extended cDNAs encoding secreted polypeptides or fragments thereof make up 5% or more of the number of nucleic acid inserts in the backbone molecules are "enriched recombinant extended cDNAs" as defined herein. Likewise, extended cDNAs encoding secreted polypeptides or fragments thereof which are in a population of plasmids in which one or more extended cDNAs of the present invention have been inserted such that they represent 5% or more of the number of inserts in the plasmid backbone are "enriched recombinant extended cDNAs" as defined herein. However, extended

cDNAs encoding secreted polypeptides or fragments thereof which are in cDNA libraries in which the extended cDNAs encoding secreted polypeptides or fragments thereof constitute less than 5% of the number of nucleic acid inserts in the population of backbone molecules, such as libraries in which backbone molecules having a cDNA insert encoding a secreted polypeptide are extremely rare, are not "enriched recombinant extended cDNAs."

In particular, the present invention relates to extended cDNAs which were derived from genes encoding secreted proteins. As used herein, a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal peptides in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g. soluble proteins), or partially (e.g. receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are 10 transported across the membrane of the endoplasmic reticulum.

Extended cDNAs encoding secreted proteins may include nucleic acid sequences, called signal sequences, which encode signal puptides which direct the extracellular secretion of the proteins encoded by the extended cDNAs. Generally, the signal peptides are located at the amino termini of secreted proteins.

Secreted proteins are translated by ribosomes associated with the "rough" endoplasmic reticulum. Generally, 15 secreted proteins are co-translationally transferred to the membrane of the endoplasmic reticulum. Association of the ribosome with the endoplasmic reticulum during translation of secreted proteins is mediated by the signal peptide. The signal peptide is typically cleaved following its co-translational entry into the endoplasmic reticulum. After delivery to the endoplasmic reticulum, secreted proteins may proceed through the Golgi apparatus. In the Golgi apparatus, the proteins may undergo post-translational modification before entering secretory vesicles which transport them across the cell membrane.

The extended cDNAs of the present invention have several important applications. For example, they may be used to express the entire secreted protein which they encode. Alternatively, they may be used to express portions of the secreted protein. The portions may comprise the signal peptides encoded by the extended cDNAs or the mature proteins encoded by the extended cDNAs (i.e. the proteins generated when the signal peptide is cleaved off). The 25 portions may also comprise polypeptides having at least 10 consecutive amino acids encoded by the extended cDNAs. Alternatively, the portions may comprise at least 15 consecutive amino acids encoded by the extended cDNAs. In some embodiments, the portions may comprise at least 25 consecutive amino acids encoded by the extended cDNAs. In other embodiments, the portions may comprise at least 40 amino acids encoded by the extended cDNAs.

Antibodies which specifically recognize the entire secreted proteins encoded by the extended cDNAs or 30 fragments thereof having at least 10 consecutive amino acids, at least 15 consecutive amino acids, at least 25 consecutive amino acids, or at least 40 consecutive amino acids may also be obtained as described below. Antibodies which specifically recognize the mature protein generated when the signal peptide is cleaved may also be obtained as described below. Similarly, antibodies which specifically recognize the signal peptides encoded by the extended cDNAs may also be obtained.

In some embodiments, the extended cDNAs include the signal sequence. In other embodiments, the extended cDNAs may include the full coding sequence for the mature protein (i.e. the protein generated when the signal polypeptide is cleaved off). In addition, the extended cDNAs may include regulatory regions upstream of the translation start site or downstream of the stop codon which control the amount, location, or developmental stage of gene expression. As discussed above, secreted proteins are therapeutically important. Thus, the proteins expressed from the cDNAs may be useful in treating or controlling a variety of human conditions. The extended cDNAs may also be used to obtain the corresponding genomic DNA. The term "corresponding genomic DNA" refers to the genomic DNA which encodes mRNA which includes the sequence of one of the strands of the extended cDNA in which thymidine residues in the sequence of the extended cDNA are replaced by uracil residues in the mRNA.

The extended cDNAs or genomic DNAs obtained therefrom may be used in forensic procedures to identify individuals or in diagnostic procedures to identify individuals having genetic diseases resulting from abnormal expression of the genes corresponding to the extended cDNAs. In addition, the present invention is useful for constructing a high resolution map of the human chromosomes.

The present invention also relates to secretion vectors capable of directing the secretion of a protein of
interest. Such vectors may be used in gene therapy strategies in which it is desired to produce a gene product in one cell which is to be delivered to another location in the body. Secretion vectors may also facilitate the purification of desired proteins.

The present invention also relates to expression vectors capable of directing the expression of an inserted gene in a desired spatial or temporal manner or at a desired level. Such vectors may include sequences upstream of the extended cDNAs such as promoters or upstream regulatory sequences.

In addition, the present invention may also be used for gene therapy to control or treat genetic diseases. Signal peptides may also be fused to heterologous proteins to direct their extracellular secretion.

One embodiment of the present invention is a purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEQ ID NOs: 40·140 and 242-377 or one of the sequences complementary thereto. In one aspect of this embodiment, the nucleic acid comprises at least 15, 25, 30, 40, 50, 75, or 100 consecutive bases of one of the sequences of SEQ ID NOs: 40·140 and 242-377 or one of the sequences complementary thereto. The nucleic acid may be a recombinant nucleic acid.

Another embodiment of the present invention is a purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ IO NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377. In one aspect of this embodiment, the nucleic acid is recombinant.

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Another embodiment of the present invention is a purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40-140 and 242-377, wherein the full coding sequence optionally comprises the sequence encoding signal peptide as well as the sequence encoding mature protein. In a preferred embodiment, the isolated or purified nucleic acid comprises the full coding sequence of one of SEQ ID Nos. 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

A further embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-140 and 242-377 which encode a mature protein. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein. In one aspect of this embodiment, the nucleic acid is recombinant.

Yet another embodiment of the present invention is a purified or isolated nucleic acid comprising the nucleotides of one of SEO ID NOs: 40-140 and 242-377 which encode the signal peptide. In a preferred embodiment, the purified or isolated nucleic acid comprises the nucleotides of SEO ID NOs: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide. In one aspect of this embodiment, the nucleic acid is recombinant.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a mature protein included in one of the sequences of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

Another embodiment of the present invention is a purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEO ID NOs: 141-241 and 378-513. In a preferred embodiment, the purified or isolated nucleic acid encodes a polypeptide having the sequence of a signal peptide included in one of the sequences of SEO ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

30 Yet another embodiment of the present invention is a purified or isolated protein comprising the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is a purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEO ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the purified or isolated polypeptide comprises at least 15, 20, 25, 35, 50, 75, 100, 150 or 200 consecutive

amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In still another aspect, the purified or isolated polypeptide comprises at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEO ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a signal peptide of one of the polypeptides of SEO ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.

Yet another embodiment of the present invention is an isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEQ ID NOs: 141-241 and 378-513. In a preferred embodiment, the isolated or purified polypeptide comprises a mature protein of one of the polypeptides of SEQ ID NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.

A further embodiment of the present invention is a method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the sequences of sequence of SEQ ID NO: 40-140 and 242-377, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the protein encoded by said cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a protein obtainable by the method described in the preceding paragraph.

Another embodiment of the present invention is a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO: 40-140 and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a mature protein obtainable by the method described in the 30 preceding paragraph.

In a preferred embodiment, the above method comprises a method of making a protein comprising the amino acid sequence of the mature protein contained in one of the sequences of SEQ ID NO: 141·145, 147, 149, 150, 152-154, 156, 157, 159·172, 176·179, 181·189, 191, 194, 195, 198, 200·226, 228, 233, 234, 236·239, 241 and 378-513, comprising the steps of obtaining a cDNA comprising one of the nucleotides sequence of sequence of SEQ ID NO:

40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode for the mature protein, inserting the cDNA in an expression vector such that the cDNA is operably linked to a promoter, and introducing the expression vector into a host cell whereby the host cell produces the mature protein encoded by the cDNA. In one aspect of this embodiment, the method further comprises the step of isolating the protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the sequence of one of SEO ID NOs: 40-140 and 242-377 or a sequence complementary thereto described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids

comprising the full coding sequences of one of SEQ ID NDs: 4D·140 and 242-377, wherein the full coding sequence
comprises the sequence encoding signal peptide and the sequence encoding mature protein described herein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID NDs: 40-140 and 242-377 which encode a mature protein which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.

Another embodiment of the present invention is a host cell containing the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID NOs: 40-140 and 242-377 which encode the signal peptide which are described herein. Preferably, the host cell contains the purified or isolated nucleic acids comprising the nucleotides of one of SEO ID Nos.: 40, 42-46, 48, 49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140 and 242-377 which encode the signal peptide.

Another embodiment of the present invention is a purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEQ ID NOs: 141-241 and 378-513. In one aspect of this embodiment, the antibody is capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NOs: 141-241 and 378-513.

Another embodiment of the present invention is an array of cDNAs or fragments thereof of at least 15 nucleotides in length which includes at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides. In one aspect of this embodiment, the array includes at least two of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides. In another aspect of this embodiment, the array includes at least five of the sequences of SEQ ID NOs: 40-140 and 242-377, the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or fragments thereof of at least 15 consecutive nucleotides.

A further embodiment of the invention encompasses purified polynucleotides comprising an insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI or a fragment thereof comprising a contiguous span of at least 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 nucleotides of said insert. An additional embodiment of the invention encompasses purified polypeptides which comprise, consist of, or consist essentially of an amino acid sequence encoded by the insert from a clone deposited in a deposit having an accession number selected from the group consisting of the accession numbers listed in Table VI, as well as polypeptides which comprise a fragment of said amino acid sequence consisting of a signal peptide, a mature protein, or a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 50, 100, or 200 amino acids encoded by said insert.

An additional embodiment of the invention encompasses purified polypeptides which comprise a contiguous span of at least 5, 8, 10, 12, 15, 20, 25, 40, 60, 100, or 200 amino acids of SEQ ID NOs: 158, 174, 175, 196, 226, 231, 232, wherein said contiguous span comprises at least one of the amino acid positions which was not shown to be identical to a public sequence in any of Figures 11 to 15. Also encompassed by the invention are purified polynuculeotides encoding said polypeptides.

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#### Brief Description of the Drawings

Figure 1 is a summary of a procedure for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

Figure 2 is an analysis of the 43 amino terminal amino acids of all human SwissProt proteins to determine the frequency of false positives and false negatives using the techniques for signal peptide identification described herein.

Figure 3 shows the distribution of von Heijne scores for 5' ESTs in each of the categories described herein and the probability that these 5' ESTs encode a signal peptide.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the categories described herein were obtained.

Figure 6 illustrates a method for obtaining extended cDNAs.

Figure 7 is a map of pED6dpc2. pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SSt cDNAs are cloned between EcoRI and Notl. PED vectors are described in Kaufman et al. 30 (1991), NAR 19: 4485-4490.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags.

Figure 9 describes the transcription factor binding sites present in each of these promoters.

Figure 10 is an alignment of the protein of SEQ ID NO: 217 with the human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEQ ID NO: 516).

Figure 11 is an alignment of the proteins of SEQ ID NOs: 174, 175 and 232 with a human secreted protein (Genseg accession number W36955, SEQ ID NO: 517).

Figure 12 is an alignment of the protein of SEQ ID NO: 231 with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515).

Figure 13 is an alignment of the protein of SEQ ID NO: 196 with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518).

Figure 14 is an alignment of the protein of SEQ ID NOs: 158 with the murine subunit 7a of the COP9 complex (Genbank accession number AF071316, SEQ ID ND: 519).

Figure 15 is an alignment of the protein of SEQ ID NO: 226 with the bovine subunit B14.5B of the NADHubiquinone oxidureductase complex (Arizmendi *et al., FEBS Lett.*, **313**: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514).

## Detailed Description of the Preferred Embodiment

#### 15 J. Obtaining 5' ESTs

The present extended cDNAs were obtained using 5' ESTs which were isolated as described below.

## A. Chemical Methods for Obtaining mRNAs having Intact 5' Ends

In order to obtain the 5' ESTs used to obtain the extended cDNAs of the present invention, mRNAs having intact 5' ends must be obtained. Currently, there are two approaches for obtaining such mRNAs. One of these 20 approaches is a chemical modification method involving derivatization of the 5' ends of the mRNAs and selection of the derivatized mRNAs. The 5' ends of eucaryotic mRNAs possess a structure referred to as a "cap" which comprises a guanosine methylated at the 7 position. The cap is joined to the first transcribed base of the mRNA by a 5', 5'. triphosphate bond. In some instances, the 5' guanosine is methylated in both the 2 and 7 positions. Rarely, the 5' guanosine is trimethylated at the 2, 7 and 7 positions. In the chemical method for obtaining mRNAs having intact 5' 25 ends, the 5' cap is specifically derivatized and coupled to a reactive group on an immobilizing substrate. This specific derivatization is based on the fact that only the ribose linked to the methylated guanosine at the 5' end of the mRNA and the ribose linked to the base at the 3' terminus of the mRNA, possess 2', 3'-cis diols. Optionally, where the 3' terminal ribose has a 2', 3'-cis diol, the 2', 3'-cis diol at the 3' end may be chemically modified, substituted, converted, or eliminated, leaving only the ribose linked to the methylated guanosine at the 5' end of the mRNA with a 2', 3'-cis diol. A 30 variety of techniques are available for eliminating the 2', 3'-cis diol on the 3' terminal ribose. For example, controlled alkaline hydrolysis may be used to generate mRNA fragments in which the 3' terminal ribose is a 3'-phosphate, 2'phosphate or (2', 3')-cyclophosphate. Thereafter, the fragment which includes the original 3' ribose may be eliminated from the mixture through chromatography on an oligo-dT column. Alternatively, a base which lacks the 2', 3'-cis diol

may be added to the 3' end of the mRNA using an RNA ligase such as T4 RNA ligase. Example 1 below describes a method for ligation of pCp to the 3' end of messenger RNA.

#### **EXAMPLE 1**

# Ligation of the Nucleoside Diphosphate pCp to the 3' End of Messenger RNA

 $1 \mu g$  of RNA was incubated in a final reaction medium of 10  $\mu l$  in the presence of 5 U of  $T_4$  phage RNA ligase in the buffer provided by the manufacturer (Gibco - BRL), 40 U of the RNase inhibitor RNasin (Promega) and, 2  $\mu l$  of  $^{32}$ pCp (Amersham #PB 10208).

The incubation was performed at 37°C for 2 hours or overnight at 7-8°C.

Following modification or elimination of the 2', 3'-cis diol at the 3' ribose, the 2', 3'-cis diol present at the 5' end of the mRNA may be oxidized using reagents such as NaBH<sub>4</sub>, NaBH<sub>3</sub>CN, or sodium periodate, thereby converting the 2', 3'-cis diol to a dialdehyde. Example 2 describes the oxidation of the 2', 3'-cis diol at the 5' end of the mRNA with sodium periodate.

#### **EXAMPLE 2**

# Dxidation of 2', 3'-cis diol at the 5' End of the mRNA

- 0.1 DD unit of either a capped oligoribonucleotide of 47 nucleotides (including the cap) or an uncapped oligoribonucleotide of 46 nucleotides were treated as follows. The oligoribonucleotides were produced by in vitro transcription using the transcription kit "AmpliScribe T7" (Epicentre Technologies). As indicated below, the DNA template for the RNA transcript contained a single cytosine. To synthesize the uncapped RNA, all four NTPs were included in the in vitro transcription reaction. To obtain the capped RNA, GTP was replaced by an analogue of the cap, m7G(5')ppp(5')G. This compound, recognized by polymerase, was incorporated into the 5' end of the nascent transcript during the step of initiation of transcription but was not capable of incorporation during the extension step.

  Consequently, the resulting RNA contained a cap at its 5' end. The sequences of the oligoribonucleotides produced by the in vitro transcription reaction were:

  + Cap:
- 25 5'm7GpppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:1)
  -Cap:
  - 5'-pppGCAUCCUACUCCCAUCCAAUUCCACCCUAACUCCUCCCAUCUCCAC-3' (SEQ ID NO:2)

The oligoribonucleotides were dissolved in 9 µl of acetate buffer (0.1 M sodium acetate, pH 5.2) and 3 µl of freshly prepared 0.1 M sodium periodate solution. The mixture was incubated for 1 hour in the dark at 4°C or room temperature. Thereafter, the reaction was stopped by adding 4 µl of 10% ethylene glycol. The product was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against water.

The resulting aldehyde groups may then be coupled to molecules having a reactive amine group, such as hydrazine, carbazide, thiocarbazide or semicarbazide groups, in order to facilitate enrichment of the 5' ends of the mRNAs. Molecules having reactive amine groups which are suitable for use in selecting mRNAs having intact 5' ends

include avidin, proteins, antibodies, vitamins, ligands capable of specifically binding to receptor molecules, or oligonucleotides. Example 3 below describes the coupling of the resulting dialdehyde to biotin.

#### **EXAMPLE 3**

#### Coupling of the Dialdehyde with Biotin

The oxidation product obtained in Example 2 was dissolved in 50  $\mu$ l of sodium acetate at a pH of between 5 and 5.2 and 50  $\mu$ l of freshly prepared 0.02 M solution of biotin hydrazide in a methoxyethanol/water mixture (1:1) of formula:

$$\begin{array}{c|c} & & & & \\ & & & \\ & & & \\ NH_2-NH-C-(CH_2)_n-NH-C-(CH_2)_4 \end{array}$$

In the compound used in these experiments, n = 5. However, it will be appreciated that other commercially available hydrazides may also be used, such as molecules of the formula above in which n varies from 0 to 5.

The mixture was then incubated for 2 hours at 37°C. Following the incubation, the mixture was precipitated with ethanol and dialyzed against distilled water.

Example 4 demonstrates the specificity of the biotinylation reaction.

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#### **EXAMPLE 4**

#### Specificity of Biotinylation

The specificity of the biotinylation for capped mRNAs was evaluated by gel electrophoresis of the following samples:

- Sample 1. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2 and labeled with <sup>32</sup>pCp as described in Example 1.
  - Sample 2. The 46 nucleotide uncapped in vitro transcript prepared as in Example 2, labeled with <sup>32</sup>pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.
- Sample 3. The 47 nucleotide capped in vitro transcript prepared as in Example 2 and labeled with <sup>32</sup>pCp as described in Example 1.
  - Sample 4. The 47 nucleotide capped in vitro transcript prepared as in Example 2, labeled with <sup>32</sup>pCp as described in Example 1, treated with the oxidation reaction of Example 2, and subjected to the biotinylation conditions of Example 3.
- Samples 1 and 2 had indentical migration rates, demonstrating that the uncapped RNAs were not oxidized and 30 biotinylated. Sample 3 migrated more slowly than Samples 1 and 2, while Sample 4 exhibited the slowest migration.

The difference in migration of the RNAs in Samples 3 and 4 demonstrates that the capped RNAs were specifically biotinylated.

In some cases, mRNAs having intact 5' ends may be enriched by binding the molecule containing a reactive amine group to a suitable solid phase substrate such as the inside of the vessel containing the mRNAs, magnetic beads, chromatography matrices, or nylon or nitrocellulose membranes. For example, where the molecule having a reactive amine group is biotin, the solid phase substrate may be coupled to avidin or streptavidin. Alternatively, where the molecule having the reactive amine group is an antibody or receptor ligand, the solid phase substrate may be coupled to the cognate antigen or receptor. Finally, where the molecule having a reactive amine group comprises an oligonucleotide, the solid phase substrate may comprise a complementary oligonucleotide.

The mRNAs having intact 5' ends may be released from the solid phase following the enrichment procedure.

For example, where the dialdehyde is coupled to biotin hydrazide and the solid phase comprises streptavidin, the mRNAs may be released from the solid phase by simply heating to 95 degrees Celsius in 2% SDS. In some methods, the molecule having a reactive amine group may also be cleaved from the mRNAs having intact 5' ends following enrichment.

Example 5 describes the capture of biotinylated mRNAs with streptavidin coated beads and the release of the biotinylated mRNAs from the beads following enrichment.

#### **EXAMPLE 5**

# Capture and Release of Biotinylated mRNAs Using Strepatividin Coated Beads

The streptavidin-coated magnetic beads were prepared according to the manufacturer's instructions (CPG Inc., USA). The biotinylated mRNAs were added to a hybridization buffer (1.5 M NaCl, pH 5 · 6). After incubating for 30 minutes, the unbound and nonbiotinylated material was removed. The beads were washed several times in water with 1% SDS. The beads obtained were incubated for 15 minutes at 95°C in water containing 2% SDS.

Example 6 demonstrates the efficiency with which biotinylated mRNAs were recovered from the streptavidin coated beads.

#### **EXAMPLE 6**

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## Efficiency of Recovery of Biotinylated mRNAs

The efficiency of the recovery procedure was evaluated as follows. RNAs were labeled with  $^{32}pCp$ , oxidized, biotinylated and bound to streptavidin coated beads as described above. Subsequently, the bound RNAs were incubated for 5, 15 or 30 minutes at 95°C in the presence of 2% SDS.

The products of the reaction were analyzed by electrophoresis on 12% polyacrylamide gels under denaturing conditions (7 M urea). The gels were subjected to autoradiography. During this manipulation, the hydrazone bonds were not reduced.

Increasing amounts of nucleic acids were recovered as incubation times in 2% SOS increased, demonstrating that biotinylated mRNAs were efficiently recovered.

In an alternative method for obtaining mRNAs having intact 5' ends, an oligonucleotide which has been derivatized to contain a reactive amine group is specifically coupled to mRNAs having an intact cap. Preferably, the 3' end of the mRNA is blocked prior to the step in which the aldehyde groups are joined to the derivatized oligonucleotide, as described above, so as to prevent the derivatized oligonucleotide from being joined to the 3' end of the mRNA. For example, pCp may be attached to the 3' end of the mRNA using T4 RNA ligase. However, as discussed above, blocking the 3' end of the mRNA is an optional step. Derivatized oligonucleotides may be prepared as described below in Example 7.

#### **EXAMPLE 7**

#### Derivatization of the Dligonucleotide

An oligonucleotide phosphorylated at its 3' end was converted to a 3' hydrazide in 3' by treatment with an aqueous solution of hydrazine or of dihydrazide of the formula  $H_2N(R1)NH_2$  at about 1 to 3 M, and at pH 4.5, in the presence of a carbodiimide type agent soluble in water such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide at a final concentration of 0.3 M at a temperature of 8°C overnight.

The derivatized oligonucleotide was then separated from the other agents and products using a standard technique for isolating oligonucleotides.

As discussed above, the mRNAs to be enriched may be treated to eliminate the 3' DH groups which may be present thereon. This may be accomplished by enzymatic ligation of sequences lacking a 3' DH, such as pCp, as described above in Example 1. Alternatively, the 3' DH groups may be eliminated by alkaline hydrolysis as described in Example 8 below.

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#### **EXAMPLE 8**

#### Alkaline Hydrolysis of mRNA

The mRNAs may be treated with alkaline hydrolysis as follows. In a total volume of  $100\mu$ l of 0.1N sodium hydroxide,  $1.5\mu$ g mRNA is incubated for 40 to 60 minutes at 4°C. The solution is neutralized with acetic acid and precipitated with ethanol.

Following the optional elimination of the 3' DH groups, the diol groups at the 5' ends of the mRNAs are oxidized as described below in Example 9.

#### **EXAMPLE 9**

#### Oxidation of Diols

Up to 1 0D unit of RNA was dissolved in 9  $\mu$ l of buffer (0.1 M sodium acetate, pH 6-7 or water) and 3  $\mu$ l of freshly prepared 0.1 M sodium periodate solution. The reaction was incubated for 1 h in the dark at 4°C or room temperature. Following the incubation, the reaction was stopped by adding 4  $\mu$ l of 10% ethylene glycol. Thereafter the mixture was incubated at room temperature for 15 minutes. After ethanol precipitation, the product was resuspended in 10 $\mu$ l or more of water or appropriate buffer and dialyzed against water.

Following oxidation of the diol groups at the 5' ends of the mRNAs, the derivatized oligonucleotide was joined to the resulting aldehydes as described in Example 10.

#### **EXAMPLE 10**

# Reaction of Aldehydes with Derivatized Oligonucleotides

The oxidized mRNA was dissolved in an acidic medium such as 50 µl of sodium acetate pH 4-6. 50 µl of a solution of the derivatized oligonucleotide was added such that an mRNA:derivatized oligonucleotide ratio of 1:20 was obtained and mixture was reduced with a borohydride. The mixture was allowed to incubate for 2 h at 37°C or overnight (14 h) at 10°C. The mixture was ethanol precipitated, resuspended in 10µl or more of water or appropriate buffer and dialyzed against distilled water. If desired, the resulting product may be analyzed using acrylamide gel electrophoresis, HPLC analysis, or other conventional techniques.

Following the attachment of the derivatized oligonucleotide to the mRNAs, a reverse transcription reaction may be performed as described in Example 11 below.

#### **EXAMPLE 11**

# Reverse Transcription of mRNAs

An oligodeoxyribonucleotide was derivatized as follows. 3 OD units of an oligodeoxyribonucleotide of sequence ATCAAGAATTCGCACGAGACCATTA (SEQ ID NO:3) having 5'-DH and 3'-P ends were dissolved in 70 µl of a 1.5 M hydroxybenzotriazole solution, pH 5.3, prepared in dimethylformamide/water (75:25) containing 2 µg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The mixture was incubated for 2 h 30 min at 22°C. The mixture was then precipitated twice in LiClO<sub>4</sub>/acetone. The pellet was resuspended in 200 µl of 0.25 M hydrazine and incubated at 8°C from 3 to 14 h. Following the hydrazine reaction, the mixture was precipitated twice in LiClO<sub>4</sub>/acetone.

The messenger RNAs to be reverse transcribed were extracted from blocks of placenta having sides of 2 cm which had been stored at -80°C. The mRNA was extracted using conventional acidic phenol techniques. Oligo-dT chromatography was used to purify the mRNAs. The integrity of the mRNAs was checked by Northern-blotting.

The diol groups on 7 µg of the placental mRNAs were oxidized as described above in Example 9. The

derivatized oligonucleotide was joined to the mRNAs as described in Example 10 above except that the precipitation step
was replaced by an exclusion chromatography step to remove derivatized oligodeoxyribonucleotides which were not
joined to mRNAs. Exclusion chromatography was performed as follows:

10 ml of AcA34 (BioSepra#230151) gel were equilibrated in 50 ml of a solution of 10 mM Tris pH 8.0, 300 mM NaCl, 1 mM EDTA, and 0.05% SDS. The mixture was allowed to sediment. The supernatant was eliminated and the gel was resuspended in 50 ml of buffer. This procedure was repeated 2 or 3 times.

A glass bead (diameter 3 mm) was introduced into a 2 ml disposable pipette (length 25 cm). The pipette was filled with the gel suspension until the height of the gel stabilized at 1 cm from the top of the pipette. The column was then equilibrated with 20 ml of equilibration buffer (10 mM Tris HCl pH 7.4, 20 mM NaCl).

10  $\mu$ l of the mRNA which had been reacted with the derivatized oligonucleotide were mixed in 39  $\mu$ l of 10 mM urea and 2  $\mu$ l of blue-glycerol buffer, which had been prepared by dissolving 5 mg of bromophenol blue in 60% glycerol (v/v), and passing the mixture through a filter with a filter of diameter 0.45  $\mu$ m.

The column was loaded. As soon as the sample had penetrated, equilibration buffer was added. 100 µl fractions were collected. Derivatized oligonucleotide which had not been attached to mRNA appeared in fraction 16 and later fractions. Fractions 3 to 15 were combined and precipitated with ethanol.

The mRNAs which had been reacted with the derivatized oligonucleotide were spotted on a nylon membrane and hybridized to a radioactive probe using conventional techniques. The radioactive probe used in these hybridizations was an oligodeoxyribonucleotide of sequence TAATGGTCTCGTGCGAATTCTTGAT (SEQ ID NO:4) which was anticomplementary to the derivatized oligonucleotide and was labeled at its 5' end with <sup>32</sup>P. 1/10th of the mRNAs which had been reacted with the derivatized oligonucleotide was spotted in two spots on the membrane and the membrane was visualized by autoradiography after hybridization of the probe. A signal was observed, indicating that the derivatized oligonucleotide had been joined to the mRNA.

The remaining 9/10 of the mRNAs which had been reacted with the derivatized oligonucleotide was reverse transcribed as follows. A reverse transcription reaction was carried out with reverse transcriptase following the manufacturer's instructions. To prime the reaction, 50 pmol of nonamers with random sequence were used.

A portion of the resulting cDNA was spotted on a positively charged nylon membrane using conventional methods. The cDNAs were spotted on the membrane after the cDNA:RNA heteroduplexes had been subjected to an alkaline hydrolysis in order to eliminate the RNAs. An oligonucleotide having a sequence identical to that of the derivatized oligonucleotide was labeled at its 5' end with <sup>32</sup>P and hybridized to the cDNA blots using conventional techniques. Single-stranded cDNAs resulting from the reverse transcription reaction were spotted on the membrane. As controls, the blot contained 1 pmol, 100 fmol, 50 fmol, 10 fmol and 1 fmol respectively of a control oligodeoxyribonucleotide of sequence identical to that of the derivatized oligonucleotide. The signal observed in the spots containing the cDNA indicated that approximately 15 fmol of the derivatized oligonucleotide had been reverse transcribed.

These results demonstrate that the reverse transcription can be performed through the cap and, in particular, that reverse transcriptase crosses the 5'-P-P-P-5' bond of the cap of eukaryotic messenger RNAs.

The single stranded cDNAs obtained after the above first strand synthesis were used as template for PCR reactions. Two types of reactions were carried out. First, specific amplification of the mRNAs for the alpha globin, dehydrogenase, pp15 and elongation factor E4 were carried out using the following pairs of oligodeoxyribonucleotide primers.

alpha-globin

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GLO-S: CCG ACA AGA CCA ACG TCA AGG CCG C (SEQ ID N0:5) GLO-As: TCA CCA GCA GGC AGT GGC TTA GGA G 3' (SEQ ID N0:6)

dehydrogenase

3 DH-S: AGT GAT TCC TGC TAC TTT GGA TGG C (SEQ ID NO:7)

3 DH-As: GCT TGG TCT TGT TCT GGA GTT TAG A (SEO ID NO:8)

pp15

PP15-S: TCC AGA ATG GGA GAC AAG CCA ATT T (SEQ ID NO:9)

5 PP15-As: AGG GAG GAG GAA ACA GCG TGA GTC C (SEQ ID ND:10)

Elongation factor E4

EFA1-S: ATG GGA AAG GAA AAG ACT CAT ATC A (SEQ ID NO:11)

EF1A-As: AGC AGC AAC AAT CAG GAC AGC ACA G (SE0 ID ND:12)

Non specific amplifications were also carried out with the antisense (\_As) oligodeoxyribonucleotides of the pairs described above and a primer chosen from the sequence of the derivatized oligodeoxyribonucleotide (ATCAAGAATTCGCACGAGACCATTA) (SEQ ID ND:13).

A 1.5% agarose gel containing the following samples corresponding to the PCR products of reverse transcription was stained with ethidium bromide. (1/20th of the products of reverse transcription were used for each PCR reaction).

- Sample 1: The products of a PCR reaction using the globin primers of SEQ ID NDs 5 and 6 in the presence of cDNA.
  - Sample 2: The products of a PCR reaction using the globin primers of SEQ ID NOs 5 and 6 in the absence of added cDNA.
- Sample 3: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the presence of cDNA.
  - Sample 4: The products of a PCR reaction using the dehydrogenase primers of SEQ ID NOs 7 and 8 in the absence of added cDNA.
  - Sample 5: The products of a PCR reaction using the pp15 primers of SEQ ID NDs 9 and 10 in the presence of cDNA.
- Sample 6: The products of a PCR reaction using the pp15 primers of SEQ ID NDs 9 and 10 in the absence of added cDNA.
  - Sample 7: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the presence of added cDNA.
- Sample 8: The products of a PCR reaction using the EIE4 primers of SEQ ID NOs 11 and 12 in the absence of added cDNA.
  - In Samples 1, 3, 5 and 7, a band of the size expected for the PCR product was observed, indicating the presence of the corresponding sequence in the cDNA population.

PCR reactions were also carried out with the antisense oligonucleotides of the globin and dehydrogenase primers (SEQ ID NOs 6 and 8) and an oligonucleotide whose sequence corresponds to that of the derivatized

oligonucleotide. The presence of PCR products of the expected size in the samples corresponding to samples 1 and 3 above indicated that the derivatized oligonucleotide had been incorporated.

The above examples summarize the chemical procedure for enriching mRNAs for those having intact 5' ends.

Further detail regarding the chemical approaches for obtaining mRNAs having intact 5' ends are disclosed in

International Application No. W096/34981, published November 7, 1996.

Strategies based on the above chemical modifications to the 5' cap structure may be utilized to generate cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived. In one version of such procedures, the 5' ends of the mRNAs are modified as described above. Thereafter, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Single stranded RNAs are eliminated to obtain a population of cDNA/mRNA heteroduplexes in which the mRNA includes an intact 5' end. The resulting heteroduplexes may be captured on a solid phase coated with a molecule capable of interacting with the molecule used to derivatize the 5' end of the mRNA. Thereafter, the strands of the heteroduplexes are separated to recover single stranded first cDNA strands which include the 5' end of the mRNA. Second strand cDNA synthesis may then proceed using conventional techniques. For example, the procedures disclosed in WO 96/34981 or in Carninci, P. et al. High-Efficiency Full-Length cDNA Cloning by Biotinylated CAP Trapper. Genomics 37:327-336 (1996) may be employed to select cDNAs which include the sequence derived from the 5' end of the coding sequence of the mRNA.

Following ligation of the oligonucleotide tag to the 5' cap of the mRNA, a reverse transcription reaction is conducted to extend a primer complementary to the mRNA to the 5' end of the mRNA. Following elimination of the RNA component of the resulting heteroduplex using standard techniques, second strand cDNA synthesis is conducted with a primer complementary to the oligonucleotide tag.

Figure 1 summarizes the above procedures for obtaining cDNAs which have been selected to include the 5' ends of the mRNAs from which they are derived.

#### B. Enzymatic Methods for Obtaining mRNAs having Intact 5' Ends

Dther techniques for selecting cDNAs extending to the 5' end of the mRNA from which they are derived are fully enzymatic. Some versions of these techniques are disclosed in Dumas Milne Edwards J.B. (Doctoral Thesis of Paris VI University, Le clonage des ADNc complets: difficultes et perspectives nouvelles. Apports pour l'etude de la regulation de l'expression de la tryptophane hydroxylase de rat, 20 Dec. 1993), EPO 625572 and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994).

Briefly, in such approaches, isolated mRNA is treated with alkaline phosphatase to remove the phosphate

groups present on the 5' ends of uncapped incomplete mRNAs. Following this procedure, the cap present on full length mRNAs is enzymatically removed with a decapping enzyme such as T4 polynucleotide kinase or tobacco acid pyrophosphatase. An oligonucleotide, which may be either a DNA oligonucleotide or a DNA-RNA hybrid oligonucleotide having RNA at its 3' end, is then ligated to the phosphate present at the 5' end of the decapped mRNA using T4 RNA

ligase. The oligonucleotide may include a restriction site to facilitate cloning of the cDNAs following their synthesis. Example 12 below describes one enzymatic method based on the doctoral thesis of Dumas.

#### **EXAMPLE 12**

### Enzymatic Approach for Dbtaining 5' ESTs

Twenty micrograms of PolyA + RNA were dephosphorylated using Calf Intestinal Phosphatase (Biolabs). After a phenol chloroform extraction, the cap structure of mRNA was hydrolysed using the Tobacco Acid Pyrophosphatase (purified as described by Shinshi et al., Biochemistry 15: 2185-2190, 1976) and a hemi 5'DNA/RNA-3' oligonucleotide having an unphosphorylated 5' end, a stretch of adenosine ribophosphate at the 3' end, and an EcoRI site near the 5' end was ligated to the 5'P ends of mRNA using the T4 RNA ligase (Biolabs). Dligonucleotides suitable for use in this procedure are preferably 30-50 bases in length. Oligonucleotides having an unphosphorylated 5' end may be synthesized by adding a fluorochrome at the 5' end. The inclusion of a stretch of adenosine ribophosphates at the 3' end of the oligonucleotide increases ligation efficiency. It will be appreciated that the oligonucleotide may contain cloning sites other than EcoRI.

Following ligation of the oligonucleotide to the phosphate present at the 5' end of the decapped mRNA, first

and second strand cDNA synthesis may be carried out using conventional methods or those specified in EPO 625,572

and Kato et al. Construction of a Human Full-Length cDNA Bank. Gene 150:243-250 (1994), and Dumas Milne Edwards,

supra. The resulting cDNA may then be ligated into vectors such as those disclosed in Kato et al. Construction of a

Human Full-Length cDNA Bank. Gene 150:243-250 (1994) or other nucleic acid vectors known to those skilled in the art

using techniques such as those described in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold

Spring Harbor Laboratory Press, 1989.

#### II. Characterization of 5' ESTs

The above chemical and enzymatic approaches for enriching mRNAs having intact 5' ends were employed to obtain 5' ESTs. First, mRNAs were prepared as described in Example 13 below.

#### **EXAMPLE 13**

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#### Preparation of mRNA

Total human RNAs or PolyA + RNAs derived from 29 different tissues were respectively purchased from LABIMO and CLDNTECH and used to generate 44 cDNA libraries as described below. The purchased RNA had been isolated from cells or tissues using acid guanidium thiocyanate-phenol-chloroform extraction (Chomczyniski, P and Sacchi, N., Analytical Biochemistry 162:156-159, 1987). PolyA + RNA was isolated from total RNA (LABIMD) by two passes of oligodT chromatography, as described by Aviv and Leder (Aviv, H. and Leder, P., Proc. Natl. Acad. Sci. USA 69:1408-1412, 1972) in order to eliminate ribosomal RNA.

The quality and the integrity of the poly A+ were checked. Northern blots hybridized with a globin probe were used to confirm that the mRNAs were not degraded. Contamination of the PolyA+ mRNAs by ribosomal sequences was checked using RNAs blots and a probe derived from the sequence of the 28S RNA. Preparations of mRNAs with less

than 5% of ribosomal RNAs were used in library construction. To avoid constructing libraries with RNAs contaminated by exogenous sequences (prokaryotic or fungal), the presence of bacterial 16S ribosomal sequences or of two highly expressed mRNAs was examined using PCR.

Following preparation of the mRNAs, the above described chemical and/or the enzymatic procedures for enriching mRNAs having intact 5' ends discussed above were employed to obtain 5' ESTs from various tissues. In both approaches an oligonucleotide tag was attached to the cap at the 5' ends of the mRNAs. The oligonucleotide tag had an EcoRI site therein to facilitate later cloning procedures.

Following attachment of the oligonucleotide tag to the mRNA by either the chemical or enzymatic methods, the integrity of the mRNA was examined by performing a Northern blot with 200-500ng of mRNA using a probe

10 complementary to the oligonucleotide tag.

#### **EXAMPLE 14**

# cDNA Synthesis Using mRNA Templates Having Intact 5' Ends

For the mRNAs joined to oligonucleotide tags using both the chemical and enzymatic methods, first strand cDNA synthesis was performed using reverse transcriptase with random nonamers as primers. In order to protect internal EcoRI sites in the cDNA from digestion at later steps in the procedure, methylated dCTP was used for first strand synthesis. After removal of RNA by an alkaline hydrolysis, the first strand of cDNA was precipitated using isopropanol in order to eliminate residual primers.

For both the chemical and the enzymatic methods, the second strand of the cDNA was synthesized with a Klenow fragment using a primer corresponding to the 5'end of the ligated oligonucleotide described in Example 12.

Preferably, the primer is 20-25 bases in length. Methylated dCTP was also used for second strand synthesis in order to protect internal EcoRI sites in the cDNA from digestion during the cloning process.

Following cDNA synthesis, the cDNAs were cloned into pBlueScript as described in Example 15 below.

#### **EXAMPLE 15**

#### Insertion of cDNAs into BlueScript

Following second strand synthesis, the ends of the cDNA were blunted with T4 DNA polymerase (Biolabs) and the cDNA was digested with EcoRI. Since methylated dCTP was used during cDNA synthesis, the EcoRI site present in the tag was the only site which was hemi-methylated. Consequently, only the EcoRI site in the oligonucleotide tag was susceptible to EcoRI digestion. The cDNA was then size fractionated using exclusion chromatography (AcA, Biosepra). Fractions corresponding to cDNAs of more than 150 bp were pooled and ethanol precipitated. The cDNA was directionally cloned into the Smal and EcoRI ends of the phagemid pBlueScript vector (Stratagene). The ligation mixture was electroporated into bacteria and propagated under appropriate antibiotic selection.

Clones containing the oligonucleotide tag attached were selected as described in Example 16 below.

#### **EXAMPLE 16**

Selection of Clones Having the Oligonucleotide Tag Attached Thereto

The plasmid DNAs containing 5' EST libraries made as described above were purified (Qiagen). A positive selection of the tagged clones was performed as follows. Briefly, in this selection procedure, the plasmid DNA was converted to single stranded DNA using gene II endonuclease of the phage F1 in combination with an exonuclease (Chang et al., Gene 127:95-8, 1993) such as exonuclease III or T7 gene 6 exonuclease. The resulting single stranded DNA was then purified using paramagnetic beads as described by Fry et al., Biotechniques, 13: 124-131, 1992. In this procedure, the single stranded DNA was hybridized with a biotinylated oligonucleotide having a sequence corresponding to the 3' end of the oligonucleotide described in Example 13. Preferably, the primer has a length of 20-25 bases. Clones including a sequence complementary to the biotinylated oligonucleotide were captured by incubation with streptavidin coated magnetic beads followed by magnetic selection. After capture of the positive clones, the plasmid DNA was released from the magnetic beads and converted into double stranded DNA using a DNA polymerase such as the ThermoSequenase obtained from Amersham Pharmacia Biotech. Alternatively, protocols such as the Gene Trapper kit (Gibco BRL) may be used. The double stranded DNA was then electroporated into bacteria. The percentage of positive clones having the 5' tag oligonucleotide was estimated to typically rank between 90 and 98% using dot blot analysis.

Following electroporation, the libraries were ordered in 384-microtiter plates (MTP). A copy of the MTP was stored for future needs. Then the libraries were transferred into 96 MTP and sequenced as described below.

#### **EXAMPLE 17**

# Sequencing of Inserts in Selected Clones

Plasmid inserts were first amplified by PCR on PE 9600 thermocyclers (Perkin-Elmer), using standard SETA-A and SETA-B primers (Genset SA), AmpliTaqGold (Perkin-Elmer), dNTPs (Boehringer), buffer and cycling conditions as recommended by the Perkin-Elmer Corporation.

PCR products were then sequenced using automatic ABI Prism 377 sequencers (Perkin Elmer, Applied Biosystems Division, Foster City, CA). Sequencing reactions were performed using PE 9600 thermocyclers (Perkin Elmer) with standard dye-primer chemistry and ThermoSequenase (Amersham Life Science). The primers used were either T7 or 21M13 (available from Genset SA) as appropriate. The primers were labeled with the JOE, FAM, ROX and TAMRA dyes. The dNTPs and ddNTPs used in the sequencing reactions were purchased from Boehringer. Sequencing buffer, reagent concentrations and cycling conditions were as recommended by Amersham.

Following the sequencing reaction, the samples were precipitated with EtOH, resuspended in formamide loading buffer, and loaded on a standard 4% acrylamide gel. Electrophoresis was performed for 2.5 hours at 3000V on an ABI 377 sequencer, and the sequence data were collected and analyzed using the ABI Prism DNA Sequencing Analysis Software, version 2.1.2.

The sequence data from the 44 cDNA libraries made as described above were transferred to a proprietary database, where quality control and validation steps were performed. A proprietary base-caller ("Trace"), working using a Unix system automatically flagged suspect peaks, taking into account the shape of the peaks, the inter-peak resolution, and the noise level. The proprietary base-caller also performed an automatic trimming. Any stretch of 25 or

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fewer bases having more than 4 suspect peaks was considered unreliable and was discarded. Sequences corresponding to cloning vector or ligation oligonucleotides were automatically removed from the EST sequences. However, the resulting EST sequences may contain 1 to 5 bases belonging to the above mentioned sequences at their 5' end. If needed, these can easily be removed on a case by case basis.

Thereafter, the sequences were transferred to the proprietary NETGENE™ Database for further analysis as described below.

Following sequencing as described above, the sequences of the 5' ESTs were entered in a proprietary database called NETGENE<sup>TM</sup> for storage and manipulation. It will be appreciated by those skilled in the art that the data could be stored and manipulated on any medium which can be read and accessed by a computer. Computer readable media include magnetically readable media, optically readable media, or electronically readable media. For example, the computer readable media may be a hard disc, a floppy disc, a magnetic tape, CD-ROM, RAM, or ROM as well as other types of other media known to those skilled in the art.

In addition, the sequence data may be stored and manipulated in a variety of data processor programs in a variety of formats. For example, the sequence data may be stored as text in a word processing file, such as

MicrosoftWORD or WORDPERFECT or as an ASCII file in a variety of database programs familiar to those of skill in the art, such as DB2, SYBASE, or DRACLE.

The computer readable media on which the sequence information is stored may be in a personal computer, a network, a server or other computer systems known to those skilled in the art. The computer or other system preferably includes the storage media described above, and a processor for accessing and manipulating the sequence data.

Once the sequence data has been stored it may be manipulated and searched to locate those stored sequences which contain a desired nucleic acid sequence or which encode a protein having a particular functional domain. For example, the stored sequence information may be compared to other known sequences to identify homologies, motifs implicated in biological function, or structural motifs.

20

Programs which may be used to search or compare the stored sequences include the MacPattern (EMBL), BLAST, and BLAST2 program series (NCBI), basic local alignment search tool programs for nucleotide (BLASTN) and peptide (BLASTX) comparisons (Altschul et al, J. Mol. Biol. 215: 403 (1990)) and FASTA (Pearson and Lipman, Proc. Natl. Acad. Sci. USA, 85: 2444 (1988)). The BLAST programs then extend the alignments on the basis of defined match and mismatch criteria.

Motifs which may be detected using the above programs include sequences encoding leucine zippers, helix-turnhelix motifs, glycosylation sites, ubiquitination sites, alpha helices, and beta sheets, signal sequences encoding signal peptides which direct the secretion of the encoded proteins, sequences implicated in transcription regulation such as homeoboxes, acidic stretches, enzymatic active sites, substrate binding sites, and enzymatic cleavage sites.

Before searching the cDNAs in the NETGENE<sup>TM</sup> database for sequence motifs of interest, cDNAs derived from mRNAs which were not of interest were identified and eliminated from further consideration as described in Example 18 below.

#### **EXAMPLE 18**

#### 5

# Elimination of Undesired Sequences from Further Consideration

5' ESTs in the NETGENE™ database which were derived from undesired sequences such as transfer RNAs, ribosomal RNAs, mitochondrial RNAs, procaryotic RNAs, fungal RNAs, Alu sequences, L1 sequences, or repeat sequences were identified using the FASTA and BLASTN programs with the parameters listed in Table II.

To eliminate 5' ESTs encoding tRNAs from further consideration, the 5' EST sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. The comparison was performed using FASTA on both strands of the 5' ESTs. Sequences having more than 80% homology over more than 60 nucleotides were identified as tRNA. Of the 144,341 sequences screened, 26 were identified as tRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding rRNAs from further consideration, the 5' EST sequences were compared to the sequences of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S = 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as rRNAs. Of the 144,341 sequences screened, 3,312 were identified as rRNAs and eliminated from further consideration.

To eliminate 5' ESTs encoding mtRNAs from further consideration, the 5' EST sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. The comparison was performed using BLASTN on both strands of the 5' ESTs with the parameter S= 108. Sequences having more than 80% homology over stretches longer than 40 nucleotides were identified as mtRNAs. Of the 144,341 sequences screened, 6,110 were identified as mtRNAs and eliminated from further consideration.

Sequences which might have resulted from exogenous contaminants were eliminated from further consideration by comparing the 5' EST sequences to release 46 of the EMBL bacterial and fungal divisions using BLASTN with the parameter S = 144. All sequences having more than 90% homology over at least 40 nucleotides were identified as exogenous contaminants. Of the 42 cDNA libraries examined, the average percentages of procaryotic and fungal sequences contained therein were 0.2% and 0.5% respectively. Among these sequences, only one could be identified as a sequence specific to fungi. The others were either fungal or procaryotic sequences having homologies with vertebrate sequences or including repeat sequences which had not been masked during the electronic comparison.

In addition, the 5' ESTs were compared to 6093 Alu sequences and 1115 L1 sequences to mask 5' ESTs containing such repeat sequences from further consideration. 5' ESTs including THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats were also eliminated from further consideration. On average, 11.5% of

the sequences in the libraries contained repeat sequences. Of this 11.5%, 7% contained Alu repeats, 3.3% contained L1 repeats and the remaining 1.2% were derived from the other types of repetitive sequences which were screened. These percentages are consistent with those found in cDNA libraries prepared by other groups. For example, the cDNA libraries of Adams et al. contained between 0% and 7.4% Alu repeats depending on the source of the RNA which was

The sequences of those 5' ESTs remaining after the elimination of undesirable sequences were compared with 5 used to prepare the cDNA library (Adams et al., Nature 377:174, 1996). the sequences of known human mRNAs to determine the accuracy of the sequencing procedures described above.

Measurement of Sequencing Accuracy by Comparison to Known Sequences To further determine the accuracy of the sequencing procedure described above, the sequences of 5' ESTs derived from known sequences were identified and compared to the known sequences. First, a FASTA analysis with overhangs shorter than 5 bp on both ends was conducted on the 5' ESTs to identify those matching an entry in the public human mRNA database. The 6655 5' ESTs which matched a known human mRNA were then realigned with their cognate mRNA and dynamic programming was used to include substitutions, insertions, and deletions in the list of 10

15 "errors" which would be recognized. Errors occurring in the last 10 bases of the 5' EST sequences were ignored to This analysis revealed that the sequences incorporated in the NETGENETM database had an accuracy of more avoid the inclusion of spurious cloning sites in the analysis of sequencing accuracy.

To determine the efficiency with which the above selection procedures select cDNAs which include the 5' ends

20 of their corresponding mRNAs, the following analysis was performed.

To determine the efficiency at which the above selection procedures isolated 5' ESTs which included sequences close to the 5' end of the mRNAs from which they were derived, the sequences of the ends of the 5' ESTs which were derived from the elongation factor 1 subunit  $\alpha$  and ferritin heavy chain genes were compared to the known convariances for these genes. Since the transcription start sites for the elongation factor 1 subunit  $\alpha$  and ferriting heavy chain are well characterized, they may be used to determine the percentage of 5' ESTs derived from these genes

For both genes, more than 95% of the cDNAs included sequences close to or upstream of the 5' end of the which included the authentic transcription start sites. To extend the analysis of the reliability of the procedures for isolating 5' ESTs from ESTs in the NETGENETM corresponding mRNAs.

database, a similar analysis was conducted using a database composed of human mRNA sequences extracted from

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sequences available in the GenBank database are deduced from genomic sequences, a 5' end matching with these sequences will be counted as an internal match. Thus, the method used here underestimates the yield of ESTs including the authentic 5' ends of their corresponding mRNAs.

The EST libraries made above included multiple 5' ESTs derived from the same mRNA. The sequences of such 5 5' ESTs were compared to one another and the longest 5' ESTs for each mRNA were identified. Overlapping cDNAs were assembled into continuous sequences (contigs). The resulting continuous sequences were then compared to public databases to gauge their similarity to known sequences, as described in Example 21 below.

Clustering of the 5' ESTs and Calculation of Novelty Indices for cDNA Libraries 10 For each sequenced EST library, the sequences were clustered by the 5' end. Each sequence in the library was compared to the others with BLASTN2 (direct strand, parameters S = 107). ESTs with High Scoring Segment Pairs

(HSPs) at least 25 bp long, having 95% identical bases and beginning closer than 10 bp from each EST 5' end were grouped. The longest sequence found in the cluster was used as representative of the cluster. A global clustering

between libraries was then performed leading to the definition of super-contigs. 15

To assess the yield of new sequences within the EST libraries, a novelty rate (NR) was defined as: NR = 100X (Number of new unique sequences found in the library/Total number of sequences from the library). Typically, novelty rating range between 10% and 41% depending on the tissue from which the EST library was obtained. For most of the

libraries, the random sequencing of 5' EST libraries was pursued until the novelty rate reached 20%.

Following characterization as described above, the collection of 5' ESTs in NETGENETM was screened to 20 identify those 5' ESTs bearing potential signal sequences as described in Example 22 below.

# Identification of Potential Signal Sequences in 5' ESTs

The 5' ESTs in the NETGENETM database were screened to identify those having an uninterrupted open reading frame (DRF) longer than 45 nucleotides beginning with an ATG codon and extending to the end of the EST.

Approximately half of the cDNA sequences in NETGENE<sup>TM</sup> contained such an DRF. The DRFs of these 5' ESTs were

searched to identify potential signal motifs using slight modifications of the procedures disclosed in Von Heijne, G. A New Method for Predicting Signal Sequence Cleavage Sites. Nucleic Acids Res. 14:4683-4690 (1986). Those 5' EST

sequences encoding a 15 amino acid long stretch with a score of at least 3.5 in the Von Heijne signal pentide

Identification matrix were considered to possess a signal sequence. Those 5' ESTs which matched a known human mRNA or EST sequence and had a 5' end more than 20 nucleotides downstream of the known 5' end were excluded SIGNALTAGTM.

from further analysis. The remaining cDNAs having signal sequences therein were included in a database called

To confirm the accuracy of the above method for identifying signal sequences, the analysis of Example 22 was performed.

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#### **EXAMPLE 23**

#### Confirmation of Accuracy of Identification of Potential Signal Sequences in 5' ESTs

The accuracy of the above procedure for identifying signal sequences encoding signal peptides was evaluated by applying the method to the 43 amino terminal amino acids of all human SwissProt proteins. The computed Von Heijne score for each protein was compared with the known characterization of the protein as being a secreted protein or a non-secreted protein. In this manner, the number of non-secreted proteins having a score higher than 3.5 (false positives) and the number of secreted proteins having a score lower than 3.5 (false negatives) could be calculated.

Using the results of the above analysis, the probability that a peptide encoded by the 5' region of the mRNA is in fact a genuine signal peptide based on its Von Heijne's score was calculated based on either the assumption that 10% of human proteins are secreted or the assumption that 20% of human proteins are secreted. The results of this analysis are shown in Figures 2 and 3.

Using the above method of identifying secretory proteins, 5' ESTs for human glucagon, gamma interferon induced monokine precursor, secreted cyclophilin-like protein, human pleiotropin, and human biotinidase precursor all of which are polypeptides which are known to be secreted, were obtained. Thus, the above method successfully identified those 5' ESTs which encode a signal peptide.

To confirm that the signal peptide encoded by the 5' ESTs actually functions as a signal peptide, the signal sequences from the 5' ESTs may be cloned into a vector designed for the identification of signal peptides. Some signal peptide identification vectors are designed to confer the ability to grow in selective medium on host cells which have a signal sequence operably inserted into the vector. For example, to confirm that a 5' EST encodes a genuine signal peptide, the signal sequence of the 5' EST may be inserted upstream and in frame with a non-secreted form of the yeast invertase gene in signal peptide selection vectors such as those described in U.S. Patent No. 5,536,637. Growth of host cells containing signal sequence selection vectors having the signal sequence from the 5' EST inserted therein confirms that the 5' EST encodes a genuine signal peptide.

Alternatively, the presence of a signal peptide may be confirmed by cloning the extended cDNAs obtained using the ESTs into expression vectors such as pXT1 (as described below), or by constructing promoter-signal sequence-reporter gene vectors which encode fusion proteins between the signal peptide and an assayable reporter protein. After introduction of these vectors into a suitable host cell, such as COS cells or NIH 3T3 cells, the growth medium may be harvested and analyzed for the presence of the secreted protein. The medium from these cells is compared to the medium from cells containing vectors lacking the signal sequence or extended cDNA insert to identify vectors which encode a functional signal peptide or an authentic secreted protein.

Those 5' ESTs which encoded a signal peptide, as determined by the method of Example 22 above, were further grouped into four categories based on their homology to known sequences. The categorization of the 5' ESTs is described in Example 24 below.

# Categorization of 5' ESTs Encoding a Signal Peptide

Those 5' ESTs having a sequence not matching any known vertebrate sequence nor any publicly available EST sequence were designated "new." Of the sequences in the SIGNALTAG $^{TM}$  database, 947 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs having a sequence not matching any vertebrate sequence but matching a publicly known EST were designated "EST-ext", provided that the known EST sequence was extended by at least 40 nucleotides in the 5' direction. Of the sequences in the SIGNALTAG<sup>TM</sup> database, 150 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those ESTs not matching any vertebrate sequence but matching a publicly known EST without extending the known EST by at least 40 nucleotides in the 5' direction were designated "EST." Of the sequences in the SIGNALTAG<sup>TM</sup> database, 599 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category.

Those 5' ESTs matching a human mRNA sequence but extending the known sequence by at least 40 nucleotides in the 5' direction were designated "VERT-ext." Of the sequences in the SIGNALTAG™ database, 23 of the 5' ESTs having a Von Heijne's score of at least 3.5 fell into this category. Included in this category was a 5' EST which extended the known sequence of the human translocase mRNA by more than 200 bases in the 5' direction. A 5' EST which extended the sequence of a human tumor suppressor gene in the 5' direction was also identified.

Figure 4 shows the distribution of 5' ESTs in each category and the number of 5' ESTs in each category having a given minimum von Heijne's score.

Each of the 5' ESTs was categorized based on the tissue from which its corresponding mRNA was obtained, as described below in Example 25.

#### **EXAMPLE 25**

# Categorization of Expression Patterns

Figure 5 shows the tissues from which the mRNAs corresponding to the 5' ESTs in each of the above described categories were obtained.

In addition to categorizing the 5' ESTs by the tissue from which the cDNA library in which they were first identified was obtained, the spatial and temporal expression patterns of the mRNAs corresponding to the 5' ESTs, as well as their expression levels, may be determined as described in Example 26 below. Characterization of the spatial and temporal expression patterns and expression levels of these mRNAs is useful for constructing expression vectors capable of producing a desired level of gene product in a desired spatial or temporal manner, as will be discussed in more detail below.

In addition, 5' ESTs whose corresponding mRNAs are associated with disease states may also be identified. For example, a particular disease may result from lack of expression, over expression, or under expression of an mRNA corresponding to a 5' EST. By comparing mRNA expression patterns and quantities in samples taken from healthy

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individuals with those from individuals suffering from a particular disease, 5' ESTs responsible for the disease may be

It will be appreciated that the results of the above characterization procedures for 5' ESTs also apply to identified. extended cDNAs (obtainable as described below) which contain sequences adjacent to the 5' ESTs. It will also be 5 appreciated that if it is desired to defer characterization until extended cDNAs have been obtained rather than characterizing the ESTs themselves, the above characterization procedures can be applied to characterize the extended cDNAs after their isolation.

# **EXAMPLE 26**

# Evaluation of Expression Levels and Patterns of mRNAs

# Corresponding to 5' ESTs or Extended cDNAs

10

Expression levels and patterns of mRNAs corresponding to 5' ESTs or extended cDNAs (obtainable as described below) may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277. Briefly, a 5' EST, extended cDNA, or fragment thereof corresponding to the gene encoding the mRNA to be characterized is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 15 or SP6) RNA polymerase promoter to produce antisense RNA. Preferably, the 5' EST or extended cDNA has 100 or more nucleotides. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with 20 ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline

The 5' ESTs, extended cDNAs, or fragments thereof may also be tagged with nucleotide sequences for the phosphatase. 25 serial analysis of gene expression (SAGE) as disclosed in UK Patent Application No. 2 305 241 A. In this method, cDNAs are prepared from a cell, tissue, organism or other source of nucleic acid for which it is desired to determine gene expression patterns. The resulting cDNAs are separated into two pools. The cDNAs in each pool are cleaved with a first restriction endonuclease, called an "anchoring enzyme," having a recognition site which is likely to be present at least once in most cDNAs. The fragments which contain the 5' or 3' most region of the cleaved cDNA are isolated by binding 30 to a capture medium such as streptavidin coated beads. A first oligonucleotide linker having a first sequence for hybridization of an amplification primer and an internal restriction site for a "tagging endonuclease" is ligated to the digested cDNAs in the first pool. Digestion with the second endonuclease produces short "tag" fragments from the cDNAs.

A second oligonucleotide having a second sequence for hybridization of an amplification primer and an internal restriction site is ligated to the digested cDNAs in the second pool. The cDNA fragments in the second pool are also digested with the "tagging endonuclease" to generate short "tag" fragments derived from the cDNAs in the second pool. The "tags" resulting from digestion of the first and second pools with the anchoring enzyme and the tagging 5 endonuclease are ligated to one another to produce "ditags." In some embodiments, the ditags are concatamerized to produce ligation products containing from 2 to 200 ditags. The tag sequences are then determined and compared to the sequences of the 5' ESTs or extended cDNAs to determine which 5' ESTs or extended cDNAs are expressed in the cell, tissue, organism, or other source of nucleic acids from which the tags were derived. In this way, the expression pattern of the 5' ESTs or extended cDNAs in the cell, tissue, organism, or other source of nucleic acids is obtained.

10 Quantitative analysis of gene expression may also be performed using arrays. As used herein, the term array means a one dimensional, two dimensional, or multidimensional arrangement of full length cDNAs (i.e. extended cDNAs twhich include the coding sequence for the signal peptide, the coding sequence for the mature protein, and a stop codon), extended cDNAs, 5' ESTs or fragments of the full length cDNAs, extended cDNAs, or 5' ESTs of sufficient length to permit specific detection of gene expression. Preferably, the fragments are at least 15 nucleotides in length. More preferably, the fragments are at least 100 nucleotides in length. More preferably, the fragments are more than 100 nucleotides in length. In some embodiments the fragments may be more than 500 nucleotides in length.

For example, quantitative analysis of gene expression may be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in a complementary DNA microarray as described by Schena et al. (Science 270:467-470, 1995; Proc. Natl. Acad. Sci. U.S.A. 93:10614-10619, 1996). Full length cDNAs, extended cDNAs, 5' 20 ESTs or fragments thereof are amplified by PCR and arrayed from 96-well microtiter plates onto silylated microscope slides using high-speed robotics. Printed arrays are incubated in a humid chamber to allow rehydration of the array elements and rinsed, once in 0.2% SDS for 1 min, twice in water for 1 min and once for 5 min in sodium borohydride solution. The arrays are submerged in water for 2 min at 95°C, transferred into 0.2% SDS for 1 min, rinsed twice with water, air dried and stored in the dark at 25°C.

25 Cell or tissue mRNA is isolated or commercially obtained and probes are prepared by a single round of reverse transcription. Probes are hybridized to 1 cm $^2$  microarrays under a 14 x 14 mm glass coverslip for 6-12 hours at  $60^{\circ}$ C. Arrays are washed for 5 min at 25°C in low stringency wash buffer (1 x SSC/0.2% SDS), then for 10 min at room temperature in high stringency wash buffer (0.1 x SSC/0.2% SDS). Arrays are scanned in 0.1 x SSC using a fluorescence laser scanning device fitted with a custom filter set. Accurate differential expression measurements are obtained by taking the average of the ratios of two independent hybridizations.

Quantitative analysis of the expression of genes may also be performed with full length cDNAs, extended cDNAs, 5' ESTs, or fragments thereof in complementary DNA arrays as described by Pietu et al. (Genome Research 6:492-503, 1996). The full length cDNAs, extended cDNAs, 5' ESTs or fragments thereof are PCR amplified and spotted on membranes. Then, mRNAs originating from various tissues or cells are labeled with radioactive nucleotides. PCT/IB98/02122 WO 99/31236

After hybridization and washing in controlled conditions, the hybridized mRNAs are detected by phospho-imaging or autoradiography. Duplicate experiments are performed and a quantitative analysis of differentially expressed mRNAs is then performed.

Alternatively, expression analysis of the 5' ESTs or extended cDNAs can be done through high density nucleotide arrays as described by Lockhart et al. (Nature Biotechnology 14: 1675-1680, 1996) and Sosnowsky et al. (Proc. Natl. Acad. Sci. 94:1119-1123, 1997). Oligonucleotides of 15-50 nucleotides corresponding to sequences of the 5' ESTs or extended cDNAs are synthesized directly on the chip (Lockhart et al., *supra*) or synthesized and then addressed to the chip (Sosnowski et al., *supra*). Preferably, the oligonucleotides are about 20 nucleotides in length.

cDNA probes labeled with an appropriate compound, such as biotin, digoxigenin or fluorescent dye, are synthesized from the appropriate mRNA population and then randomly fragmented to an average size of 50 to 100 nucleotides. The said probes are then hybridized to the chip. After washing as described in Lockhart et al., supra and application of different electric fields (Sosnowsky et al., Proc. Natl. Acad. Sci. 94:1119-1123)., the dyes or labeling compounds are detected and quantified. Duplicate hybridizations are performed. Comparative analysis of the intensity of the signal originating from cDNA probes on the same target oligonucleotide in different cDNA samples indicates a differential expression of the mRNA corresponding to the 5' EST or extended cDNA from which the oligonucleotide sequence has been designed.

# III. Use of 5' ESTs to Clone Extended cDNAs and to Clone the Corresponding Genomic DNAs

Once 5' ESTs which include the 5' end of the corresponding mRNAs have been selected using the procedures described above, they can be utilized to isolate extended cDNAs which contain sequences adjacent to the 5' ESTs. The extended cDNAs may include the entire coding sequence of the protein encoded by the corresponding mRNA, including the authentic translation start site, the signal sequence, and the sequence encoding the mature protein remaining after cleavage of the signal peptide. Such extended cDNAs are referred to herein as "full length cDNAs." Alternatively, the extended cDNAs may include only the sequence encoding the mature protein remaining after cleavage of the signal peptide, or only the sequence encoding the signal peptide.

Example 27 below describes a general method for obtaining extended cDNAs. Example 28 below describes the cloning and sequencing of several extended cDNAs, including extended cDNAs which include the entire coding sequence and authentic 5' end of the corresponding mRNA for several secreted proteins.

25

The methods of Examples 27, 28, and 29 can also be used to obtain extended cDNAs which encode less than the entire coding sequence of the secreted proteins encoded by the genes corresponding to the 5' ESTs. In some embodiments, the extended cDNAs isolated using these methods encode at least 10 amino acids of one of the proteins encoded by the sequences of SEO ID NOs: 40·140 and 242·377. In further embodiments, the extended cDNAs encode at least 20 amino acids of the proteins encoded by the sequences of SEO ID NOs: 40·140 and 242·377. In further embodiments, the extended cDNAs encode at least 30 amino amino acids of the sequences of SEO ID NOs: 40·140 and

242-377. In a preferred embodiment, the extended cDNAs encode a full length protein sequence, which includes the protein coding sequences of SEQ ID NOs: 40-140 and 242-377.

## **EXAMPLE 27**

# General Method for Using 5' ESTs to Clone and Sequence Extended cDNAs

5 The following general method has been used to quickly and efficiently isolate extended cDNAs including sequence adjacent to the sequences of the 5' ESTs used to obtain them. This method may be applied to obtain extended cDNAs for any 5' EST in the NETGENE™ database, including those 5' ESTs encoding secreted proteins. The method is summarized in Figure 6.

# 1. Obtaining Extended cDNAs

# 10 a) First strand synthesis

The method takes advantage of the known 5' sequence of the mRNA. A reverse transcription reaction is conducted on purified mRNA with a poly 14dT primer containing a 49 nucleotide sequence at its 5' end allowing the addition of a known sequence at the end of the cDNA which corresponds to the 3' end of the mRNA. For example, the primer may have the following sequence: 5'-ATC GTT GAG ACT CGT ACC AGC AGA GTC ACG AGA GAG ACT ACA CGG 15 TAC TGG TTT TTT TTT TTT TTVN -3' (SEQ ID NO:14). Those skilled in the art will appreciate that other sequences may also be added to the poly dT sequence and used to prime the first strand synthesis. Using this primer and a reverse transcriptase such as the Superscript II (Gibco BRL) or Rnase H Minus M-MLV (Promega) enzyme, a reverse transcript anchored at the 3' polyA site of the RNAs is generated.

After removal of the mRNA hybridized to the first cDNA strand by alkaline hydrolysis, the products of the 20 alkaline hydrolysis and the residual poly dT primer are eliminated with an exclusion column such as an AcA34 (Biosepra) matrix as explained in Example 11.

# b) Second strand synthesis

A pair of nested primers on each end is designed based on the known 5' sequence from the 5' EST and the known 3' end added by the poly dT primer used in the first strand synthesis. Software used to design primers are either 25 based on GC content and melting temperatures of oligonucleotides, such as DSP (Illier and Green, PCR Meth. Appl. 1:124-128, 1991), or based on the octamer frequency disparity method (Griffais et al., Nucleic Acids Res. 19: 3887-3891, 1991 such as PC-Rare (http://bioinformatics.weizmann.ac.il/software/PC-Rare/doc/manuel.html).

Preferably, the nested primers at the  $5^{\circ}$  end are separated from one another by four to nine bases. The  $5^{\circ}$ primer sequences may be selected to have melting temperatures and specificities suitable for use in PCR.

30 Preferably, the nested primers at the 3' end are separated from one another by four to nine bases. For example, the nested 3' primers may have the following sequences: (5'- CCA GCA GAG TCA CGA GAG AGA CTA CAC GG -3'(SEQ ID NO:15), and 5'- CAC GAG AGA GAC TAC ACG GTA CTG G -3' (SEQ ID NO:16). These primers were selected because they have melting temperatures and specificities compatible with their use in PCR. However, those skilled in the art will appreciate that other sequences may also be used as primers.

The first PCR run of 25 cycles is performed using the Advantage Tth Polymerase Mix (Clontech) and the outer primer from each of the nested pairs. A second 20 cycle PCR using the same enzyme and the inner primer from each of the nested pairs is then performed on 1/2500 of the first PCR product. Thereafter, the primers and nucleotides are removed.

# 5 2. Sequencing of Full Length Extended cDNAs or Fragments Thereof

Due to the lack of position constraints on the design of 5' nested primers compatible for PCR use using the OSP software, amplicons of two types are obtained. Preferably, the second 5' primer is located upstream of the translation initiation codon thus yielding a nested PCR product containing the whole coding sequence. Such a full length extended cDNA undergoes a direct cloning procedure as described in section a below. However, in some cases, the second 5' primer is located downstream of the translation initiation codon, thereby yielding a PCR product containing only part of the ORF. Such incomplete PCR products are submitted to a modified procedure described in section b below.

# a) Nested PCR products containing complete ORFs

When the resulting nested PCR product contains the complete coding sequence, as predicted from the 5'EST sequence, it is cloned in an appropriate vector such as pED6dpc2, as described in section 3.

# b) Nested PCR products containing incomplete ORFs

When the amplicon does not contain the complete coding sequence, intermediate steps are necessary to obtain both the complete coding sequence and a PCR product containing the full coding sequence. The complete coding sequence can be assembled from several partial sequences determined directly from different PCR products as described in the following section.

Once the full coding sequence has been completely determined, new primers compatible for PCR use are designed to obtain amplicons containing the whole coding region. However, in such cases, 3' primers compatible for PCR use are located inside the 3' UTR of the corresponding mRNA, thus yielding amplicons which lack part of this region, i.e. the polyA tract and sometimes the polyadenylation signal, as illustrated in figure 6. Such full length extended cDNAs are then cloned into an appropriate vector as described in section 3.

## c) Sequencing extended cDNAs

Sequencing of extended cDNAs is performed using a Die Terminator approach with the AmpliTaq DNA polymerase FS kit available from Perkin Elmer.

In order to sequence PCR fragments, primer walking is performed using software such as OSP to choose primers and automated computer software such as ASMG (Sutton et al., *Genome Science Technol.* 1: 9-19, 1995) to construct contigs of walking sequences including the initial 5' tag using minimum overlaps of 32 nucleotides. Preferably, primer walking is performed until the sequences of full length cDNAs are obtained.

Completion of the sequencing of a given extended cDNA fragment is assessed as follows. Since sequences located after a polyA tract are difficult to determine precisely in the case of uncloned products, sequencing and primer

walking processes for PCR products are interrupted when a polyA tract is identified in extended cDNAs obtained as described in case b. The sequence length is compared to the size of the nested PCR product obtained as described above. Due to the limited accuracy of the determination of the PCR product size by gel electrophoresis, a sequence is considered complete if the size of the obtained sequence is at least 70 % the size of the first nested PCR product. If the length of the sequence determined from the computer analysis is not at least 70% of the length of the nested PCR product, these PCR products are cloned and the sequence of the insertion is determined. When Northern blot data are available, the size of the mRNA detected for a given PCR product is used to finally assess that the sequence is complete. Sequences which do not fulfill the above criteria are discarded and will undergo a new isolation procedure.

Sequence data of all extended cDNAs are then transferred to a proprietary database, where quality controls and validation steps are carried out as described in example 15.

# 3. Cloning of Full Length Extended cDNAs

The PCR product containing the full coding sequence is then cloned in an appropriate vector. For example, the extended cDNAs can be cloned into the expression vector pED6dpc2 (DiscoverEase, Genetics Institute, Cambridge, MA) as follows. The structure of pED6dpc2 is shown in Figure 7. pED6dpc2 vector DNA is prepared with blunt ends by performing an EcoRl digestion followed by a fill in reaction. The blunt ended vector is dephosphorylated. After removal of PCR primers and ethanol precipitation, the PCR product containing the full coding sequence or the extended cDNA obtained as described above is phosphorylated with a kinase subsequently removed by phenol-Sevag extraction and precipitation. The double stranded extended cDNA is then ligated to the vector and the resulting expression plasmid introduced into appropriate host cells.

Since the PCR products obtained as described above are blunt ended molecules that can be cloned in either direction, the orientation of several clones for each PCR product is determined. Then, 4 to 10 clones are ordered in microtiter plates and subjected to a PCR reaction using a first primer located in the vector close to the cloning site and a second primer located in the portion of the extended cDNA corresponding to the 3' end of the mRNA. This second primer may be the antisense primer used in anchored PCR in the case of direct cloning (case a) or the antisense primer located inside the 3'UTR in the case of indirect cloning (case b). Clones in which the start codon of the extended cDNA is operably linked to the promoter in the vector so as to permit expression of the protein encoded by the extended cDNA are conserved and sequenced. In addition to the ends of cDNA inserts, approximately 50 bp of vector DNA on each side of the cDNA insert are also sequenced.

The cloned PCR products are then entirely sequenced according to the aforementioned procedure. In this case, contig assembly of long fragments is then performed on walking sequences that have already contigated for uncloned PCR products during primer walking. Sequencing of cloned amplicons is complete when the resulting contigs include the whole coding region as well as overlapping sequences with vector DNA on both ends.

# 4. Computer Analysis of Full Length Extended cDNA

Sequences of all full length extended cDNAs are then submitted to further analysis as described below and using the parameters found in Table II with the following modifications. For screening of miscellaneous subdivisions of Genbank, FASTA was used instead of BLASTN and 15 nucleotide of homology was the limit instead of 17. For Alu detection, BLASTN was used with the following parameters: S = 72; identity = 70%; and length = 40 nucleotides.

- Polyadenylation signal and polyA tail which were not search for the 5' ESTs were searched. For polyadenylation signal detection the signal (AATAAA) was searched with one permissible mismatch in the last ten nucleotides preceding the 5' end of the polyA. For the polyA, a stretch of 8 amino acids in the last 20 nucleotides of the sequence was searched with BLAST2N in the sense strand with the following parameters (W = 6, S = 10, E = 1000, and identity = 90%). Finally, patented sequences and ORF homologies were searched using, respectively, BLASTN and BLASTP on GenSEO
- 10 (Derwent's database of patented nucleotide sequences) and SWISSPROT for ORFs with the following parameters (W = 8 and B = 10). Before examining the extended full length cDNAs for sequences of interest, extended cDNAs which are not of interest are searched as follows.

#### a) Elimination of undesired sequences

Although 5'ESTs were checked to remove contaminant sequences as described in Example 18, a last verification was carried out to identify extended cDNAs sequences derived from undesired sequences such as vector RNAs, transfer RNAs, ribosomal rRNAs, mitochondrial RNAs, prokaryotic RNAs and fungal RNAs using the FASTA and BLASTN programs on both strands of extended cDNAs as described below.

To identify the extended cDNAs encoding vector RNAs, extended cDNAs are compared to the known sequences of vector RNA using the FASTA program. Sequences of extended cDNAs with more than 90% homology over stretches of 15 nucleotides are identified as vector RNA.

To identify the extended cDNAs encoding tRNAs, extended cDNA sequences were compared to the sequences of 1190 known tRNAs obtained from EMBL release 38, of which 100 were human. Sequences of extended cDNAs having more than 80% homology over 60 nucleotides using FASTA were identified as tRNA.

To identify the extended cDNAs encoding rRNAs, extended cDNA sequences were compared to the sequences
of 2497 known rRNAs obtained from EMBL release 38, of which 73 were human. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as rRNAs.

To identify the extended cDNAs encoding mtRNAs, extended cDNA sequences were compared to the sequences of the two known mitochondrial genomes for which the entire genomic sequences are available and all sequences transcribed from these mitochondrial genomes including tRNAs, rRNAs, and mRNAs for a total of 38 sequences. Sequences of extended cDNAs having more than 80% homology over stretches longer than 40 nucleotides using BLASTN were identified as mtRNAs.

Sequences which might have resulted from other exogenous contaminants were identified by comparing extended cDNA sequences to release 105 of Genbank bacterial and fungal divisions. Sequences of extended cDNAs

having more than 90% homology over 40 nucleotides using BLASTN were identified as exogenous prokaryotic or fungal contaminants.

In addition, extended cDNAs were searched for different repeat sequences, including Alu sequences, L1 sequences, THE and MER repeats, SSTR sequences or satellite, micro-satellite, or telomeric repeats. Sequences of 5 extended cDNAs with more than 70% homology over 40 nucleotide stretches using BLASTN were identified as repeat sequences and masked in further identification procedures. In addition, clones showing extensive homology to repeats, i.e., matches of either more than 50 nucleotides if the homology was at least 75% or more than 40 nucleotides if the homology was at least 85% or more than 30 nucleotides if the homology was at least 90%, were flagged.

### b) Identification of structural features

10 Structural features, e.g. polyA tail and polyadenylation signal, of the sequences of full length extended cDNAs are subsequently determined as follows.

A polyA tail is defined as a homopolymeric stretch of at least 11 A with at most one alternative base within it. The polyA tail search is restricted to the last 20 nt of the sequence and limited to stretches of 11 consecutive A's because sequencing reactions are often not readable after such a polyA stretch. Stretches with 100% homology over 6 15 nucleotides are identified as polyA tails.

To search for a polyadenylation signal, the polyA tail is clipped from the full-length sequence. The 50 bp preceding the polyA tail are searched for the canonic polyadenylation AAUAAA signal allowing one mismatch to account for possible sequencing errors and known variation in the canonical sequence of the polyadenylation signal.

## c) Identification of functional features

20 Functional features, e.g. ORFs and signal sequences, of the sequences of full length extended cDNAs were subsequently determined as follows.

The 3 upper strand frames of extended cDNAs are searched for ORFs defined as the maximum length fragments beginning with a translation initiation codon and ending with a stop codon. ORFs encoding at least 20 amino acids are preferred.

25 Each found ORF is then scanned for the presence of a signal peptide in the first 50 amino-acids or, where appropriate, within shorter regions down to 20 amino acids or less in the ORF, using the matrix method of von Heijne (Nuc. Acids Res. 14: 4683-4690 (1986)) and the modification described in Example 22.

## d) Homology to either nucleotidic or proteic sequences

Sequences of full length extended cDNAs are then compared to known sequences on a nucleotidic or proteic 30 basis.

Sequences of full length extended cDNAs are compared to the following known nucleic acid sequences: vertebrate sequences (Genbank), EST sequences (Genbank), patented sequences (Geneseqn) and recently identified sequences (Genbank daily releases) available at the time of filing for the priority documents. Full length cONA sequences are also compared to the sequences of a private database (Genset internal sequences) in order to find sequences that

have already been identified by applicants. Sequences of full length extended cDNAs with more than 90% homology over 30 nucleotides using either BLASTN or BLAST2N as indicated in Table III are identified as sequences that have already been described. Matching vertebrate sequences are subsequently examined using FASTA; full length extended cDNAs with more than 70% homology over 30 nucleotides are identified as sequences that have already been described.

ORFs encoded by full length extended cDNAs as defined in section c) are subsequently compared to known amino acid sequences found in Swissprot release CHP, PIR release PIR# and Genpept release GPEPT public databases using BLASTP with the parameter W - 8 and allowing a maximum of 10 matches. Sequences of full length extended cDNAs showing extensive homology to known protein sequences are recognized as already identified proteins.

In addition, the three-frame conceptual translation products of the top strand of full length extended cDNAs are compared to publicly known amino acid sequences of Swissprot using BLASTX with the parameter E=0.001. Sequences of full length extended cDNAs with more than 70% homology over 30 amino acid stretches are detected as already identified proteins.

## 5. Selection of Cloned Full Length Sequences of the Present Invention

Cloned full length extended cDNA sequences that have already been characterized by the aforementioned 15 computer analysis are then submitted to an automatic procedure in order to preselect full length extended cDNAs containing sequences of interest.

## a) Automatic sequence preselection

All complete cloned full length extended cDNAs clipped for vector on both ends are considered. First, a negative selection is operated in order to eliminate unwanted cloned sequences resulting from either contaminants or 20 PCR artifacts as follows. Sequences matching contaminant sequences such as vector RNA, tRNA, mtRNA, rRNA sequences are discarded as well as those encoding ORF sequences exhibiting extensive homology to repeats as defined in section 4 a). Sequences obtained by direct cloning using nested primers on 5' and 3' tags (section 1. case a) but lacking polyA tail are discarded. Only ORFs containing a signal peptide and ending either before the polyA tail (case a) or before the end of the cloned 3'UTR (case b) are kept. Then, ORFs containing unlikely mature proteins such as mature 25 proteins which size is less than 20 amino acids or less than 25% of the immature protein size are eliminated.

In the selection of the OFR, priority was given to the ORF and the frame corresponding to the polypeptides described in SignalTag Patents (United States Patent Application Serial Nos: 08/905,223; 08/905,135; 08/905,051; 08/905,144; 08/905,279; 08/904,468; 08/905,134; and 08/905,133). If the ORF was not found among the OFRs described in the SignalTag Patents, the ORF encoding the signal peptide with the highest score according to Von Heijne 30 method as defined in Example 22 was chosen. If the scores were identical, then the longest ORF was chosen.

Sequences of full length extended cDNA clones are then compared pairwise with BLAST after masking of the repeat sequences. Sequences containing at least 90% homology over 30 nucleotides are clustered in the same class. Each cluster is then subjected to a cluster analysis that detects sequences resulting from internal priming or from

alternative splicing, identical sequences or sequences with several frameshifts. This automatic analysis serves as a basis for manual selection of the sequences.

## b) Manual sequence selection

Manual selection is carried out using automatically generated reports for each sequenced full length extended 5 cDNA clone. During this manual procedures, a selection is operated between clones belonging to the same class as follows. ORF sequences encoded by clones belonging to the same class are aligned and compared. If the homology between nucleotidic sequences of clones belonging to the same class is more than 90% over 30 nucleotide stretches or if the homology between amino acid sequences of clones belonging to the same class is more than 80% over 20 amino acid stretches, than the clones are considered as being identical. The chosen ORF is the best one according to the 10 criteria mentioned below. If the nucleotide and amino acid homologies are less than 90% and 80% respectively, the clones are said to encode distinct proteins which can be both selected if they contain sequences of interest.

Selection of full length extended cDNA clones encoding sequences of interest is performed using the following criteria. Structural parameters (initial tag, polyadenylation site and signal) are first checked. Then, homologies with known nucleic acids and proteins are examined in order to determine whether the clone sequence match a known 15 nucleic/proteic sequence and, in the latter case, its covering rate and the date at which the sequence became public. If there is no extensive match with sequences other than ESTs or genomic DNA, or if the clone sequence brings substantial new information, such as encoding a protein resulting from alternative slicing of an mRNA coding for an already known protein, the sequence is kept. Examples of such cloned full length extended cDNAs containing sequences of interest are described in Example 28. Sequences resulting from chimera or double inserts as assessed by homology to other 20 sequences are discarded during this procedure.

### **EXAMPLE 28**

## Cloning and Sequencing of Extended cDNAs

The procedure described in Example 27 above was used to obtain the extended cDNAs of the present invention. Using this approach, the full length cDNA of SEQ ID NO:17 was obtained. This cDNA falls into the "EST-25 ext" category described above and encodes the signal peptide MKKVLLLITAILAVAVG (SEQ ID NO: 18) having a von

The full length cDNA of SEQ ID NO:19 was also obtained using this procedure. This cDNA falls into the "ESText" category described above and encodes the signal peptide MWWFQQGLSFLPSALVIWTSA (SEQ ID NO.20) having a von Heijne score of 5.5.

Another full length cDNA obtained using the procedure described above has the sequence of SEQ ID NO:21. 30 This cDNA, falls into the "EST-ext" category described above and encodes the signal peptide MVLTTLPSANSANSPVNMPTTGPNSLSYASSALSPCLT (SEQ ID NO:22) having a von Heijne score of 5.9.

30

The above procedure was also used to obtain a full length cDNA having the sequence of SEQ ID NO:23. This cDNA falls into the "EST-ext" category described above and encodes the signal peptide ILSTVTALTFAXA (SEQ ID NO:24) having a von Heijne score of 5.5.

The full length cDNA of SEQ ID NO:25 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LVLTLCTLPLAVA (SEQ ID NO:26) having a von Heijne score of 10.1.

The full length cDNA of SEQ ID NO:27 was also obtained using this procedure. This cDNA falls into the "new" category described above and encodes a signal peptide LWLLFFLVTAIHA (SEQ ID NO:28) having a von Heijne score of 10.7.

The above procedures were also used to obtain the extended cDNAs of the present invention. 5' ESTs expressed in a variety of tissues were obtained as described above. The appended sequence listing provides the tissues from which the extended cDNAs were obtained. It will be appreciated that the extended cDNAs may also be expressed in tissues other than the tissue listed in the sequence listing.

5' ESTs obtained as described above were used to obtain extended cDNAs having the sequences of SEQ ID NOs: 40·140 and 242·377. Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40·140 and 242·377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40·140 and 242·377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40·140 and 242·377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40·140 and 242·377 of stop codons (listed under the heading Stop Codon Location in Table IV), the locations in SEQ ID NOs: 40·140 and 242·377 of polyA signals (listed under the heading Poly A Signal Location in Table IV) and the locations of polyA sites (listed under the heading Poly A Site Location in Table IV).

The polypeptides encoded by the extended cDNAs were screened for the presence of known structural or functional motifs or for the presence of signatures, small amino acid sequences which are well conserved amongst the members of a protein family. The conserved regions have been used to derive consensus patterns or matrices included in the PROSITE data bank, in particular in the file prosite.dat (Release 13.0 of November 1995, located at http://expasy.hcuge.ch/sprot/prosite.html. Prosite\_convert and prosite\_scan programs (http://ulrec3.unil.ch/ftpserveur/prosite\_scan) were used to find signatures on the extended cDNAs.

For each pattern obtained with the prosite\_convert program from the prosite.dat file, the accuracy of the detection on a new protein sequence has been tested by evaluating the frequency of irrelevant hits on the population of human secreted proteins included in the data bank SWISSPROT. The ratio between the number of hits on shuffled proteins (with a window size of 20 amino acids) and the number of hits on native (unshuffled) proteins was used as an index. Every pattern for which the ration was greater than 20% (one hit on shuffled proteins for 5 hits on native

proteins) was skipped during the search with prosite\_scan. The program used to shuffle protein sequences (db\_shuffled) and the program used to determine the statistics for each pattern in the protein data banks (prosite\_statistics) are available on the ftp site http://ulrec3.unil.ch/ftpserveur/prosite\_scan.

Table V lists the sequence identification numbers of the polypeptides of SEQ IO NOs: 141-241 and 378-513,

5 the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the mature polypeptide created by cleaving the signal peptide from the full length polypeptide (fourth column).

The nucleotide sequences of the sequences of SEO ID NOs: 40·140 and 242·377 and the amino acid sequences

10 encoded by SEO ID NOs: 40·140 and 242·377 (i.e. amino acid sequences of SEO ID NOs: 141·241 and 378·513) are

provided in the appended sequence listing. In some instances, the sequences are preliminary and may include some
incorrect or ambiguous sequences or amino acids. The sequences of SEO ID NOs: 40·140 and 242·377 can readily be
screened for any errors therein and any sequence ambiguities can be resolved by resequencing a fragment containing
such errors or ambiguities on both strands. Nucleic acid fragments for resolving sequencing errors or ambiguities may be

15 obtained from the deposited clones or can be isolated using the techniques described herein. Resolution of any such
ambiguities or errors may be facilitated by using primers which hybridize to sequences located close to the ambiguous or
erroneous sequences. For example, the primers may hybridize to sequences within 50·75 bases of the ambiguity or
error. Upon resolution of an error or ambiguity, the corresponding corrections can be made in the protein sequences
encoded by the DNA containing the error or ambiguity. For example, in the sequences of the present invention, ambiguities

20 in the sequence of SEO ID NO: 131 were resolved. The amino acid sequence of the protein encoded by a particular clone
can also be determined by expression of the clone in a suitable host cell, collecting the protein, and determining its
sequence.

For each amino acid sequence, Applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing. Some of the amino acid sequences may contain "Xaa" designators. These "Xaa" designators indicate either (1) a residue which cannot be identified because of nucleotide sequence ambiguity or (2) a stop codon in the determined sequence where Applicants believe one should not exist (if the sequence were determined more accurately).

Cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377) of the present invention in the vector pED6dpc2, are maintained in permanent deposit by the inventors at Genset, S.A., 24 Rue Royale, 75008 Paris, France.

Pools of cells containing the extended cDNAs (SEQ ID NOs: 40-140 and 242-377), from which cells containing a particular polynucleotide are obtainable, were deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 or the European Collection of Cell Cultures, Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 0JG, United Kingdom. Each extended cDNA clone has been transfected into separate bacterial cells (E-

coli) for this composite deposit. Table VI lists the deposit numbers of the clones containing the extended cDNAs of the present invention. Table VII provides the internal designation number assigned to each SEQ ID NO and indicates whether the sequence is a nucleic acid sequence or a protein sequence.

Each extended cDNA can be removed from the pED6dpc2 vector in which it was deposited by performing a 5 Notl, Pstl double digestion to produce the appropriate fragment for each clone. The proteins encoded by the extended cDNAs may also be expressed from the promoter in pED6dpc2.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The design 10 of the oligonucleotide probe should preferably follow these parameters:

- (a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;
- (b) Preferably, the probe is designed to have a  $T_m$  of approx. 80°C (assuming 2 degrees for each A or T and 4 degrees for each G or C). However, probes having melting temperatures between 40 °C and 80 °C may also be used provided that specificity is not lost.

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The oligonucleotide should preferably be labeled with (-[32P]ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantified by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4X106 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100  $\mu$ l of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 ug/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing 25 ampicillin at 100 μg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 30 175.3 g NaC1/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 pg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1X106 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to

1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

The plasmid DNA obtained using these procedures may then be manipulated using standard cloning techniques familiar to those skilled in the art. Alternatively, a PCR can be done with primers designed at both ends of the extended cDNA insertion. For example, a PCR reaction may be conducted using a primer having the sequence GGCCATACACTTGAGTGAC (SEQ ID NO:38) and a primer having the sequence ATATAGACAAACGCACACC (SEQ. ID. NO:39). The PCR product which corresponds to the extended cDNA can then be manipulated using standard cloning techniques familiar to those skilled in the art.

In addition to PCR based methods for obtaining extended cDNAs, traditional hybridization based methods may also be employed. These methods may also be used to obtain the genomic DNAs which encode the mRNAs from which the 5' ESTs were derived, mRNAs corresponding to the extended cDNAs, or nucleic acids which are homologous to extended cDNAs or 5' ESTs. Example 29 below provides an example of such methods.

15

#### **EXAMPLE 29**

# Methods for Obtaining Extended cDNAs or Nucleic Acids Homologous to Extended cDNAs or 5' ESTs

A full length cDNA library can be made using the strategies described in Examples 13, 14, 15, and 16 above by replacing the random nonamer used in Example 14 with an oligo-dT primer. For instance, the oligonucleotide of SEQ ID NO:14 may be used.

Alternatively, a cDNA library or genomic DNA library may be obtained from a commercial source or made using techniques familiar to those skilled in the art. The library includes cDNAs which are derived from the mRNA corresponding to a 5' EST or which have homology to an extended cDNA or 5' EST. The cDNA library or genomic DNA library is hybridized to a detectable probe comprising at least 10 consecutive nucleotides from the 5' EST or extended cDNA using conventional techniques. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises at least 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 30 nucleotides from the 5' EST or extended cDNA. In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for identifying cDNA clones in a cDNA library which hybridize to a given probe sequence are disclosed in Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, 1989. The same techniques may be used to isolate genomic DNAs.

Briefly, cDNA or genomic DNA clones which hybridize to the detectable probe are identified and isolated for further manipulation as follows. A probe comprising at least 10 consecutive nucleotides from the 5' EST or extended

cDNA is labeled with a detectable label such as a radioisotope or a fluorescent molecule. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST or extended cDNA. More preferably, the probe comprises 20-30 consecutive nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises more than 30 nucleotides from the 5' EST or extended cDNA. In some embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST or extended cDNA.

Techniques for labeling the probe are well known and include phosphorylation with polynucleotide kinase, nick translation, in vitro transcription, and non-radioactive techniques. The cDNAs or genomic DNAs in the library are transferred to a nitrocellulose or nylon filter and denatured. After incubation of the filter with a blocking solution, the filter is contacted with the labeled probe and incubated for a sufficient amount of time for the probe to hybridize to cDNAs or genomic DNAs containing a sequence capable of hybridizing to the probe.

By varying the stringency of the hybridization conditions used to identify extended cDNAs or genomic DNAs which hybridize to the detectable probe, extended cDNAS having different levels of homology to the probe can be identified and isolated. To identify extended cDNAs or genomic DNAs having a high degree of homology to the probe sequence, the melting temperature of the probe may be calculated using the following formulas:

For probes between 14 and 70 nucleotides in length the melting temperature (Tm) is calculated using the formula: Tm=81.5+16.6(log [Na+])+0.41(fraction G+C)-(600/N) where N is the length of the probe.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation  $Tm = 81.5 + 16.6(log [Na +]) + 0.41(fraction G + C) \cdot (0.63\% formamide) \cdot (600/N)$  where N is the length of the probe.

Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 100µg denatured fragmented salmon sperm DNA, 50% formamide. The formulas for SSC and Denhardt's solutions are listed in Sambrook et al., supra.

Hybridization is conducted by adding the detectable probe to the prehybridization solutions listed above. Where the probe comprises double stranded DNA, it is denatured before addition to the hybridization solution. The filter is contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to extended cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200 nucleotides in length, the hybridization may be carried out at 15-25°C below the Tm. For shorter probes, such as oligonucleotide probes, the hybridization may be conducted at 15-25°C below the Tm. Preferably, for hybridizations in 6X SSC, the hybridization is conducted at approximately 68°C. Preferably, for hybridizations in 50% formamide containing solutions, the hybridization is conducted at approximately 42°C.

All of the foregoing hybridizations would be considered to be under "stringent" conditions. Following hybridization, the filter is washed in 2X SSC, 0.1% SDS at room temperature for 15 minutes. The filter is then washed

with 0.1X SSC, 0.5% SDS at room temperature for 30 minutes to 1 hour. Thereafter, the solution is washed at the hybridization temperature in 0.1X SSC, 0.5% SDS. A final wash is conducted in 0.1X SSC at room temperature.

Extended cDNAs, nucleic acids homologous to extended cDNAs or 5' ESTs, or genomic DNAs which have hybridized to the probe are identified by autoradiography or other conventional techniques.

The above procedure may be modified to identify extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs having decreasing levels of homology to the probe sequence. For example, to obtain extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5°C from 68°C to 42°C in a hybridization buffer having a Na+ concentration of approximately 1M. Following 10 hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate" conditions above 50°C and "low" conditions below 50°C.

Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42°C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following 15 hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50°C. These conditions are considered to be "moderate" conditions above 25% formamide and "low" conditions below 25% formamide.

Extended cDNAs, nucleic acids homologous to extended cDNAs, or genomic DNAs which have hybridized to the probe are identified by autoradiography.

If it is desired to obtain nucleic acids homologous to extended cDNAs, such as allelic variants thereof or nucleic 20 acids encoding proteins related to the proteins encoded by the extended cDNAs, the level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may readily be determined. To determine the level of homology between the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived, the nucleotide sequences of the hybridized nucleic acid and the extended cDNA or 5'EST from which the probe was derived are compared. For example, using the above methods, nucleic acids having at least 95% nucleic acid 25 homology to the extended cDNA or 5'EST from which the probe was derived may be obtained and identified. Similarly, by using progressively less stringent hybridization conditions one can obtain and identify nucleic acids having at least 90%, at least 85%, at least 80% or at least 75% homology to the extended cDNA or 5'EST from which the probe was derived. The level of homology between the hybridized nucleic acid and the extended cDNA or 5' EST used as the probe may be further determined using BLAST2N; parameters may be adapted depending on the sequence length and degree of 30 homology studied. In such comparisons, the default parameters or the parameters listed in Tables II and III may be used.

To determine whether a clone encodes a protein having a given amount of homology to the protein encoded by the extended cDNA or 5' EST, the amino acid sequence encoded by the extended cDNA or 5' EST is compared to the amino acid sequence encoded by the hybridizing nucleic acid. Homology is determined to exist when an amino acid sequence in the extended cDNA or 5' EST is closely related to an amino acid sequence in the hybridizing nucleic acid. A

sequence is closely related when it is identical to that of the extended cDNA or 5' EST or when it contains one or more amino acid substitutions therein in which amino acids having similar characteristics have been substituted for one another. Using the above methods, one can obtain nucleic acids encoding proteins having at least 95%, at least 90%, at least 85%, at least 80% or at least 75% homology to the proteins encoded by the extended cDNA or 5'EST from which the probe was derived. Using the above methods and algorithms such as FASTA with parameters depending on the sequence length and degree of homology studied the level of homology may be determined. In determining the level of homology using FASTA, the default parameters or the parameters listed in Tables II or III may be used.

Alternatively, extended cDNAs may be prepared by obtaining mRNA from the tissue, cell, or organism of interest using mRNA preparation procedures utilizing poly A selection procedures or other techniques known to those skilled in the art. A first primer capable of hybridizing to the poly A tail of the mRNA is hybridized to the mRNA and a reverse transcription reaction is performed to generate a first cDNA strand.

The first cDNA strand is hybridized to a second primer containing at least 10 consecutive nucleotides of the sequences of the 5' EST for which an extended cDNA is desired. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the sequences of the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the sequences of the 5' EST. In some embodiments, the primer comprises more than 30 nucleotides from the sequences of the 5' EST. If it is desired to obtain extended cDNAs containing the full protein coding sequence, including the authentic translation initiation site, the second primer used contains sequences located upstream of the translation initiation site. The second primer is extended to generate a second cDNA strand complementary to the first cDNA strand. Alternatively, RTPCR may be performed as described above using primers from both ends of the cDNA to be obtained.

Extended cDNAs containing 5' fragments of the mRNA may be prepared by contacting an mRNA comprising the sequence of the 5' EST for which an extended cDNA is desired with a primer comprising at least 10 consecutive nucleotides of the sequences complementary to the 5' EST, hybridizing the primer to the mRNAs, and reverse transcribing the hybridized primer to make a first cDNA strand from the mRNAs. Preferably, the primer comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More preferably, the primer comprises 20-30 consecutive nucleotides from the 5' EST.

Thereafter, a second cDNA strand complementary to the first cDNA strand is synthesized. The second cDNA strand may be made by hybridizing a primer complementary to sequences in the first cDNA strand to the first cDNA strand and extending the primer to generate the second cDNA strand.

The double stranded extended cDNAs made using the methods described above are isolated and cloned. The extended cDNAs may be cloned into vectors such as plasmids or viral vectors capable of replicating in an appropriate host cell. For example, the host cell may be a bacterial, mammalian, avian, or insect cell.

Techniques for isolating mRNA, reverse transcribing a primer hybridized to mRNA to generate a first cDNA strand, extending a primer to make a second cDNA strand complementary to the first cDNA strand, isolating the double

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stranded cDNA and cloning the double stranded cDNA are well known to those skilled in the art and are described in Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. 1997 and Sambrook et al. Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989.

Alternatively, kits for obtaining full length cDNAs, such as the GeneTrapper (Cat. No. 10356-020, Gibco, BRL),

may be used for obtaining full length cDNAs or extended cDNAs. In this approach, full length or extended cDNAs are
prepared from mRNA and cloned into double stranded phagemids. The cDNA library in the double stranded phagemids is
then rendered single stranded by treatment with an endonuclease, such as the Gene II product of the phage F1, and
Exonuclease III as described in the manual accompanying the GeneTrapper kit. A biotinylated oligonucleotide comprising
the sequence of a 5' EST, or a fragment containing at least 10 nucleotides thereof, is hybridized to the single stranded
phagemids. Preferably, the fragment comprises at least 12, 15, or 17 consecutive nucleotides from the 5' EST. More
preferably, the fragment comprises 20-30 consecutive nucleotides from the 5' EST. In some procedures, the fragment
may comprise more than 30 consecutive nucleotides from the 5' EST. For example, the fragment may comprises at least
40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the 5' EST.

Hybrids between the biotinylated oligonucleotide and phagemids having inserts containing the 5' EST sequence are isolated by incubating the hybrids with streptavidin coated paramagnetic beads and retrieving the beads with a magnet. Thereafter, the resulting phagemids containing the 5' EST sequence are released from the beads and converted into double stranded DNA using a primer specific for the 5' EST sequence. The resulting double stranded DNA is transformed into bacteria. Extended cDNAs containing the 5' EST sequence are identified by colony PCR or colony hybridization.

A plurality of extended cDNAs containing full length protein coding sequences or sequences encoding only the mature protein remaining after the signal peptide is cleaved may be provided as cDNA libraries for subsequent evaluation of the encoded proteins or use in diagnostic assays as described below.

## IV. Expression of Proteins Encoded by Extended cDNAs Isolated Using 5' ESTs

Extended cDNAs containing the full protein coding sequences of their corresponding mRNAs or portions

thereof, such as cDNAs encoding the mature protein, may be used to express the secreted proteins or portions thereof which they encode as described in Example 30 below. If desired, the extended cDNAs may contain the sequences encoding the signal peptide to facilitate secretion of the expressed protein. It will be appreciated that a plurality of extended cDNAs containing the full protein coding sequences or portions thereof may be simultaneously cloned into expression vectors to create an expression library for analysis of the encoded proteins as described below.

#### **EXAMPLE 30**

### Expression of the Proteins Encoded by Extended cDNAs or Portions Thereof

To express the proteins encoded by the extended cDNAs or portions thereof, nucleic acids containing the coding sequence for the proteins or portions thereof to be expressed are obtained as described in Examples 27-29 and cloned into a suitable expression vector. If desired, the nucleic acids may contain the sequences encoding the signal

peptide to facilitate secretion of the expressed protein. For example, the nucleic acid may comprise the sequence of one of SEQ ID NOs: 40-140 and 242-377 listed in Table IV and in the accompanying sequence listing. Alternatively, the nucleic acid may comprise those nucleotides which make up the full coding sequence of one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

lt will be appreciated that should the extent of the full coding sequence (i.e. the sequence encoding the signal peptide and the mature protein resulting from cleavage of the signal peptide) differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the full coding sequences in the sequences of SEQ ID NOs. 40-140 and 242-377.

For example, the sequence of SEQ ID NO: 115 represents an alternatively spliced transcript of a previously identified mRNA.. Accordingly, the scope of any claims herein relating to nucleic acids containing the full coding sequence of one of SEQ ID NOs. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the full coding sequences listed in Table IV Similarly, should the extent of the full length polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the amino acid sequence of the full length polypeptides is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V.

Alternatively, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the mature protein (i.e. the protein created by cleaving the signal peptide off) encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the mature protein differ from that listed 20 in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, posttranslational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the mature protein in the sequences of SEQ ID NOs. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids 25 containing the sequence encoding the mature protein encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table IV. Thus, claims relating to nucleic acids containing the sequence encoding the mature protein encompass equivalents to the sequences listed in Table IV, such as sequences encoding biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in 30 addition to cleavage of the signal peptide. Similarly, should the extent of the mature polypeptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a mature protein included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from or equivalents to the sequences listed in Table V. Thus, claims relating to polypeptides comprising the sequence of the mature protein encompass equivalents to the sequences

listed in Table IV, such as biologically active proteins resulting from post-translational modification, enzymatic cleavage, or other readily identifiable variations from or equivalents to the secreted proteins in addition to cleavage of the signal peptide. It will also be appreciated that should the biologically active form of the polypeptides included in the sequence of one of SEO IO NOs. 141-241 and 378-513 or the nucleic acids encoding the biologically active form of the polypeptides differ from those identified as the mature polypeptide in Table V or the nucleotides encoding the mature polypeptide in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the amino acids in the biologically active form of the polypeptides and the nucleic acids encoding the biologically active form of the polypeptides. In such instances, the claims relating to polypetides comprising the mature protein included in one of SEO ID NOs. 141-241 and 378-513 or nucleic acids comprising the nucleotides of one of SEO ID NOs. 40-140 and 242-377 encoding the mature protein shall not be construed to exclude any readily identifiable variations from the sequences listed in Table IV and Table V.

In some embodiments, the nucleic acid used to express the protein or portion thereof may comprise those nucleotides which encode the signal peptide encoded by one of the sequences of SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above.

It will be appreciated that should the extent of the sequence encoding the signal peptide differ from that listed in Table IV as a result of a sequencing error, reverse transcription or amplification error, mRNA splicing, post-translational modification of the encoded protein, enzymatic cleavage of the encoded protein, or other biological factors, one skilled in the art would be readily able to identify the extent of the sequence encoding the signal peptide in the sequences of SEQ ID Nos. 40-140 and 242-377. Accordingly, the scope of any claims herein relating to nucleic acids containing the sequence encoding the signal peptide encoded by one of SEQ ID Nos. 40-140 and 242-377 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table IV. Similarly, should the extent of the signal peptides differ from those indicated in Table V as a result of any of the preceding factors, the scope of claims relating to polypeptides comprising the sequence of a signal peptide included in the sequence of one of SEQ ID NOs. 141-241 and 378-513 is not to be construed as excluding any readily identifiable variations from the sequences listed in Table V.

Alternatively, the nucleic acid may encode a polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the nucleic acid may encode a polypeptide comprising at least 15 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 25 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the nucleic acid may encode a polypeptide comprising at least 60, at least 75, at least 100 or more than 100 consecutive amino acids of one of the sequences of SEQ ID Nos: 141-241 and 378-513.

The nucleic acids inserted into the expression vectors may also contain sequences upstream of the sequences encoding the signal peptide, such as sequences which regulate expression levels or sequences which confer tissue specific expression.

The nucleic acid encoding the protein or polypeptide to be expressed is operably linked to a promoter in an expression vector using conventional cloning technology. The expression vector may be any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence may be optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767.

The following is provided as one exemplary method to express the proteins encoded by the extended cDNAs corresponding to the 5' ESTs or the nucleic acids described above. First, the methionine initiation codon for the gene and the poly A signal of the gene are identified. If the nucleic acid encoding the polypeptide to be expressed lacks a methionine to serve as the initiation site, an initiating methionine can be introduced next to the first codon of the nucleic acid using conventional techniques. Similarly, if the extended cDNA lacks a poly A signal, this sequence can be added to the construct by, for example, splicing out the Poly A signal from pSG5 (Stratagene) using Bgll and Sall restriction endonuclease enzymes and incorporating it into the mammalian expression vector pXT1 (Stratagene). pXT1 contains the LTRs and a portion of the gag gene from Moloney Murine Leukemia Virus. The position of the LTRs in the construct allow efficient stable transfection. The vector includes the Herpes Simplex Thymidine Kinase promoter and the selectable neomycin gene. The extended cDNA or portion thereof encoding the polypeptide to be expressed is obtained by PCR from the bacterial vector using oligonucleotide primers complementary to the extended cDNA or portion thereof and containing restriction endonuclease sequences for Pst I incorporated into the 5' primer and Bglll at the 5' end of the corresponding cDNA 3' primer, taking care to ensure that the extended cDNA is positioned in frame with the poly A signal. The purified fragment obtained from the resulting PCR reaction is digested with PstI, blunt ended with an exonuclease, digested with Bgl II, purified and ligated to pXT1, now containing a poly A signal and digested with BglII.

The ligated product is transfected into mouse NIH 3T3 cells using Lipofectin (Life Technologies, Inc., Grand Island, New York) under conditions outlined in the product specification. Positive transfectants are selected after growing the transfected cells in 600ug/ml G418 (Sigma, St. Louis, Missouri). Preferably the expressed protein is released into the culture medium, thereby facilitating purification.

Alternatively, the extended cDNAs may be cloned into pED6dpc2 as described above. The resulting pED6dpc2 constructs may be transfected into a suitable host cell, such as COS 1 cells. Methotrexate resistant cells are selected and expanded. Preferably, the protein expressed from the extended cDNA is released into the culture medium thereby facilitating purification.

Proteins in the culture medium are separated by gel electrophoresis. If desired, the proteins may be ammonium sulfate precipitated or separated based on size or charge prior to electrophoresis.

As a control, the expression vector lacking a cDNA insert is introduced into host cells or organisms and the proteins in the medium are harvested. The secreted proteins present in the medium are detected using techniques such as Coomassie or silver staining or using antibodies against the protein encoded by the extended cDNA. Coomassie and silver staining techniques are familiar to those skilled in the art.

Antibodies capable of specifically recognizing the protein of interest may be generated using synthetic 15-mer peptides having a sequence encoded by the appropriate 5' EST, extended cDNA, or portion thereof. The synthetic peptides are injected into mice to generate antibody to the polypeptide encoded by the 5' EST, extended cDNA, or portion thereof.

Secreted proteins from the host cells or organisms containing an expression vector which contains the extended cDNA derived from a 5' EST or a portion thereof are compared to those from the control cells or organism. The presence of a band in the medium from the cells containing the expression vector which is absent in the medium from the control cells indicates that the extended cDNA encodes a secreted protein. Generally, the band corresponding to the protein encoded by the extended cDNA will have a mobility near that expected based on the number of amino acids in the open reading frame of the extended cDNA. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

Alternatively, if the protein expressed from the above expression vectors does not contain sequences directing its secretion, the proteins expressed from host cells containing an expression vector containing an insert encoding a secreted protein or portion thereof can be compared to the proteins expressed in host cells containing the expression vector without an insert. The presence of a band in samples from cells containing the expression vector with an insert which is absent in samples from cells containing the expression vector without an insert indicates that the desired protein or portion thereof is being expressed. Generally, the band will have the mobility expected for the secreted protein or portion thereof. However, the band may have a mobility different than that expected as a result of modifications such as glycosylation, ubiquitination, or enzymatic cleavage.

The protein encoded by the extended cDNA may be purified using standard immunochromatography techniques. In such procedures, a solution containing the secreted protein, such as the culture medium or a cell extract, is applied to a column having antibodies against the secreted protein attached to the chromatography matrix. The secreted protein is allowed to bind the immunochromatography column. Thereafter, the column is washed to remove non-specifically bound proteins. The specifically bound secreted protein is then released from the column and recovered using standard techniques.

If antibody production is not possible, the extended cDNA sequence or portion thereof may be incorporated into expression vectors designed for use in purification schemes employing chimeric polypeptides. In such strategies the coding sequence of the extended cDNA or portion thereof is inserted in frame with the gene encoding the other half of

the chimera. The other half of the chimera may be β-globin or a nickel binding polypeptide encoding sequence. A chromatography matrix having antibody to β-globin or nickel attached thereto is then used to purify the chimeric protein. Protease cleavage sites may be engineered between the β-globin gene or the nickel binding polypeptide and the extended cDNA or portion thereof. Thus, the two polypeptides of the chimera may be separated from one another by protease digestion.

One useful expression vector for generating  $\beta$ -globin chimerics is pSG5 (Stratagene), which encodes rabbit  $\beta$ -globin. Intron II of the rabbit  $\beta$ -globin gene facilitates splicing of the expressed transcript, and the polyadenylation signal incorporated into the construct increases the level of expression. These techniques as described are well known to those skilled in the art of molecular biology. Standard methods are published in methods texts such as Davis et al.,

(Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro Express<sup>TM</sup> Translation Kit (Stratagene).

Following expression and purification of the secreted proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof, the purified proteins may be tested for the ability to bind to the surface of various cell types as described in Example 31 below. It will be appreciated that a plurality of proteins expressed from these cDNAs may be included in a panel of proteins to be simultaneously evaluated for the activities specifically described below, as well as other biological roles for which assays for determining activity are available.

#### **EXAMPLE 31**

20 <u>Analysis of Secreted Proteins to Determine Whether they Bind to the Cell Surface</u>

The proteins encoded by the 5' ESTs, extended cDNAs, or fragments thereof are cloned into expression vectors such as those described in Example 30. The proteins are purified by size, charge, immunochromatography or other techniques familiar to those skilled in the art. Following purification, the proteins are labeled using techniques known to those skilled in the art. The labeled proteins are incubated with cells or cell lines derived from a variety of organs or tissues to allow the proteins to bind to any receptor present on the cell surface. Following the incubation, the cells are washed to remove non-specifically bound protein. The labeled proteins are detected by autoradiography. Alternatively, unlabeled proteins may be incubated with the cells and detected with antibodies having a detectable label, such as a fluorescent molecule, attached thereto.

Specificity of cell surface binding may be analyzed by conducting a competition analysis in which various amounts of unlabeled protein are incubated along with the labeled protein. The amount of labeled protein bound to the cell surface decreases as the amount of competitive unlabeled protein increases. As a control, various amounts of an unlabeled protein unrelated to the labeled protein is included in some binding reactions. The amount of labeled protein bound to the cell surface does not decrease in binding reactions containing increasing amounts of unrelated unlabeled protein, indicating that the protein encoded by the cDNA binds specifically to the cell surface.

As discussed above, secreted proteins have been shown to have a number of important physiological effects and, consequently, represent a valuable therapeutic resource. The secreted proteins encoded by the extended cDNAs or portions thereof made according to Examples 27-29 may be evaluated to determine their physiological activities as described below.

#### 5 EXAMPLE 32

Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Cytokine, Cell Proliferation or Cell Differentiation Activity

As discussed above, secreted proteins may act as cytokines or may affect cellular proliferation or differentiation. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B5, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7c and CMK. The proteins encoded by the above extended cDNAs or portions thereof may be evaluated for their ability to regulate T cell or thymocyte proliferation in assays such as those described above or in the following references: Current Protocols in Immunology, Ed. by J.E. Coligan et al., Greene Publishing Associates and Wiley-Interscience; Takai et al. J. Immunol. 137:3494-3500, 1986. Bertagnolli et al. J. Immunol. 145:1706-1712, 1990. Bertagnolli et al., Cellular Immunology 133:327-341, 1991. Bertagnolli, et al. J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152:1756-1761, 1994.

In addition, numerous assays for cytokine production and/or the proliferation of spleen cells, lymph node cells
and thymocytes are known. These include the techniques disclosed in Current Protocols in Immunology. J.E. Coligan
et al. Eds., Vol 1 pp. 3.12.1-3.12.14 John Wiley and Sons, Toronto. 1994; and Schreiber, R.D. Current Protocols in
Immunology., supra Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be assayed for the ability to regulate the proliferation and differentiation of hematopoietic or lymphopoietic cells. Many assays for such activity are familiar to those skilled in the art, including the assays in the following references: Bottomly, K., Davis, L.S. and Lipsky, P.E., Measurement of Human and Murine Interleukin 2 and Interleukin 4, Current Protocols in Immunology., J.E. Coligan et al. Eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 36:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Nordan, R., Measurement of Mouse and Human Interleukin 6 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Bennett, F., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Human Interleukin 11 Current Protocols in Immunology. J.E. Coligan et al. Eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J., Measurement of Mouse and Human Interleukin 9 Current Protocols in Immunology. J.E. Coligan et al., Eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

The proteins encoded by the cDNAs may also be assayed for their ability to regulate T-cell responses to antigens. Many assays for such activity are familiar to those skilled in the art, including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function), Chapter 6 (Cytokines and Their Cellular Receptors) and Chapter 7, (Immunologic Studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Those proteins which exhibit cytokine, cell proliferation, or cell differentiation activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which induction of cell proliferation or differentiation is beneficial. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 33**

## Assaying the Proteins Expressed from Extended cDNAs or Portions

## Thereof for Activity as Immune System Regulators

The proteins encoded by the cDNAs may also be evaluated for their effects as immune regulators. For example, the proteins may be evaluated for their activity to influence thymocyte or splenocyte cytotoxicity. Numerous assays for such activity are familiar to those skilled in the art including the assays described in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte Function 3.1-3.19) and Chapter 7 (Immunologic studies in Humans) in Current Protocols in Immunology, J.E. Coligan et al. Eds, Greene Publishing Associates and Wiley-Interscience; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

The proteins encoded by the cDNAs may also be evaluated for their effects on T-cell dependent immunoglobulin responses and isotype switching. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Maliszewski, J. Immunol. 144:3028-3033, 1990; Mond, J.J. and Brunswick, M Assays for B Cell Function: *In vitro* Antibody Production, Vol 1 pp. 3.8.1-3.8.16 in Current Protocols in Immunology. J.E. Coligan et al Eds., John Wiley and Sons, Toronto. 1994.

The proteins encoded by the cDNAs may also be evaluated for their effect on immune effector cells, including their effect on Th1 cells and cytotoxic lymphocytes. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 3 (In Vitro Assays for Mouse Lymphocyte

Function 3.1-3.19) and Chapter 7 (Immunologic Studies in Humans) in **Current Protocols in Immunology**, J.E. Coligan et al. Eds., Greene Publishing Associates and Wiley-Interscience; Takai et al., **J. Immunol**. 137:3494-3500, 1986; Takai et al., **J. Immunol**. 140:508-512, 1988; Bertagnolli et al., **J. Immunol**. 149:3778-3783, 1992.

The proteins encoded by the cDNAs may also be evaluated for their effect on dendritic cell mediated activation of naive T-cells. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

The proteins ercoded by the cDNAs may also be evaluated for their influence on the lifetime of lymphocytes.

Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Those proteins which exhibit activity as immune system regulators activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of immune activity is beneficial. For example, the protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCIO)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis,

myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to regulate immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T-cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. 10 Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally,

tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

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Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte 15 antigen functions (such as, for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 20 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an 25 immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed 30 using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4lg fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models

of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which 5 promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead 10 to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/pr/pr mice or NZB hybrid mice, murine autoimmuno collagen arthritis, diabetes mellitus in OD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory 20 form of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to T cells 25 in vivo, thereby activating the T cells.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (e.g., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be 30 transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acids encoding all or a portion of (e.g., a cytoplasmic domain truncated portion) of an MHC class I α chain protein and β<sub>2</sub> macroglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class II or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain,can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 34**

# Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Hematopoiesis Regulating Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their hematopoiesis regulating activity. For example, the effect of the proteins on embryonic stem cell differentiation may be evaluated. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915. 1993.

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their influence on the lifetime of stem cells and stem cell differentiation. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Freshney, M.G. Methylcellulose Colony Forming Assays, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; McNiece, I.K. and Briddell, R.A. Primitive Hematopoietic Colony Forming Cells with High Proliferative Potential, in Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Ploemacher, R.E. Cobblestone Area Forming Cell Assay, In Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Spooncer, E., Dexter, M. and Allen, T. Long Term Bone Marrow Cultures in the Presence of Stromal Cells, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds.

pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; and Sutherland, H.J. Long Term Culture Initiating Cell Assay, in Culture of Hematopoietic Cells. R.I. Freshney, et al. Eds. pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Those proteins which exhibit hematopoiesis regulatory activity may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of hematopoeisis is beneficial. For example, a protein of the present 5 invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid 10 cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelosuppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem 15 cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantion, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or 20 genetically manipulated for gene therapy. Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 35**

#### Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Tissue Growth

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effect on tissue growth. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in International Patent Publication No. W095/16035, International Patent Publication No. W095/05846 and International Patent Publication No. W091/07491.

Assays for wound healing activity include, without limitation, those described in: Winter, <u>Epidermal Wound</u>

30 <u>Healing</u>, pps. 71-112 (Maibach, H1 and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Those proteins which are involved in the regulation of tissue growth may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of tissue growth is beneficial. For example, a protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or

nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

15 Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to 20 tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate 25 growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e., for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as

Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium) muscle

(smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to generate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokinc damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

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#### **EXAMPLE 36**

## Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Regulation of Reproductive Hormones or Cell Movement

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their ability to regulate reproductive hormones, such as follicle stimulating hormone. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986. Chapter 6.12 (Measurement of Alpha and Beta Chemokines) Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Intersciece; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al. Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

Those proteins which exhibit activity as reproductive hormones or regulators of cell movement may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of reproductive hormones or cell movement are beneficial. For example, a protein of the present invention may also exhibit activin- or inhibin-related

activities. Inhibins are characterized by their ability to inhibit the release of folicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of folic stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin B group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 36A**

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## Assaying the Proteins Expressed from Extended cDNAs or

## Portions Thereof for Chemotactic/Chemokinetic Activity

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for chemotactic/chemokinetic activity. For example, a protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, cosinophils, epithelial and/or endothelial cells. Chemotactic and chmokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhension of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12,

Measurement of alpha and beta Chemokincs 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Mueller et al Eur. J. Immunol. 25:1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153:1762-1768, 1994.

#### **EXAMPLE 37**

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#### Assaying the Proteins Expressed from Extended cDNAs or

#### Portions Thereof for Regulation of Blood Clotting

The proteins encoded by the extended cDNAs or portions thereof may also be evaluated for their effects on blood clotting. Numerous assays for such activity are familiar to those skilled in the art, including the assays disclosed in the following references: Linet et al., **J. Clin. Pharmacol.** 26:131·140, 1986; Burdick et al., **Thrombosis Res.**10 45:413-419, 1987; Humphrey et al., **Fibrinolysis** 5:71-79 (1991); Schaub, **Prostaglandins** 35:467-474, 1988.

Those proteins which are involved in the regulation of blood clotting may then be formulated as pharmaceuticals and used to treat clinical conditions in which regulation of blood clotting is beneficial. For example, a protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulations disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as,for example, infarction of cardiac and central nervous system vessels (e.g., stroke). Alternatively, as described in more detail below, genes encoding these proteins or nucleic acids regulating the expression of these proteins may be introduced into appropriate host cells to increase or decrease the expression of the proteins as desired.

#### **EXAMPLE 38**

## Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Involvement in Receptor/Ligand Interactions

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for their involvement in receptor/ligand interactions. Numerous assays for such involvement are familiar to those skilled in the art, including the assays disclosed in the following references: Chapter 7.28 (Measurement of Cellular Adhesion under Static Conditions 7.28.1-7.28.22) in Current Protocols in Immunology, J.E. Coligan et al. Eds. Greene Publishing Associates and Wiley-Interscience; Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160, 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995; Gyuris et al., Cell 75:791-803, 1993.

For example, the proteins of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion

molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune respones). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

#### **EXAMPLE 38A**

# Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Anti-Inflammatory Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusioninury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

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#### **EXAMPLE 38B**

# Assaying the Proteins Expressed from Extended cDNAs or Portions Thereof for Tumor Inhibition Activity

The proteins encoded by the extended cDNAs or a portion thereof may also be evaluated for tumor inhibition activity. In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, climinating or inhibiting factors, agents or cell types which promote tumor growth.

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or

circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or climination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

#### **EXAMPLE 39**

## Identification of Proteins which Interact with Polypeptides Encoded by Extended cDNAs

Proteins which interact with the polypeptides encoded by extended cDNAs or portions thereof, such as

receptor proteins, may be identified using two hybrid systems such as the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech). As described in the manual accompanying the Matchmaker Two Hybrid System 2 (Catalog No. K1604-1, Clontech), the extended cDNAs or portions thereof, are inserted into an expression vector such that they are in frame with DNA encoding the DNA binding domain of the yeast transcriptional activator GAL4. cDNAs in a cDNA library which encode proteins which might interact with the polypeptides encoded by the extended cDNAs or portions thereof are inserted into a second expression vector such that they are in frame with DNA encoding the activation domain of GAL4. The two expression plasmids are transformed into yeast and the yeast are plated on selection medium which selects for expression of selectable markers on each of the expression vectors as well as GAL4 dependent expression of the HIS3 gene. Transformants capable of growing on medium lacking histidine are screened for GAL4 dependent lacZ expression. Those cells which are positive in both the histidine selection and the lacZ assay contain plasmids encoding proteins which interact with the polypeptide encoded by the extended cDNAs or portions thereof.

Alternatively, the system described in Lustig et al., Methods in Enzymology 283: 83-99 (1997) may be used for identifying molecules which interact with the polypeptides encoded by extended cDNAs. In such systems, *in vitro* transcription reactions are performed on a pool of vectors containing extended cDNA inserts cloned downstream of a promoter which drives *in vitro* transcription. The resulting pools of mRNAs are introduced into *Xenopus laevis* oocytes.

30 The oocytes are then assayed for a desired acitivity.

Alternatively, the pooled *in vitro* transcription products produced as described above may be translated *in vitro*. The pooled *in vitro* translation products can be assayed for a desired activity or for interaction with a known polypeptide.

Proteins or other molecules interacting with polypeptides encoded by extended cDNAs can be found by a variety of additional techniques. In one method, affinity columns containing the polypeptide encoded by the extended cDNA or a portion thereof can be constructed. In some versions, of this method the affinity column contains chimeric proteins in which the protein encoded by the extended cDNA or a portion thereof is fused to glutathione S-transferase. 5 A mixture of cellular proteins or pool of expressed proteins as described above and is applied to the affinity column. Proteins interacting with the polypeptide attached to the column can then be isolated and analyzed on 2-D electrophoresis gel as described in Ramunsen et al. Electrophoresis, 18, 588-598 (1997). Alternatively, the proteins retained on the affinity column can be purified by electrophoresis based methods and sequenced. The same method can be used to isolate antibodies, to screen phage display products, or to screen phage display human antibodies.

Proteins interacting with polypeptides encoded by extended cDNAs or portions thereof can also be screened by using an Optical Biosensor as described in Edwards & Leatherbarrow, Analytical Biochemistry, 246, 1-6 (1997). The main advantage of the method is that it allows the determination of the association rate between the protein and other interacting molecules. Thus, it is possible to specifically select interacting molecules with a high or low association rate. Typically a target molecule is linked to the sensor surface (through a carboxymethl dextran matrix) and a sample of test 15 molecules is placed in contact with the target molecules. The binding of a test molecule to the target molecule causes a change in the refractive index and/ or thickness. This change is detected by the Biosensor provided it occurs in the evanescent field (which extend a few hundred manometers from the sensor surface). In these screening assays, the target molecule can be one of the polypeptides encoded by extended cDNAs or a portion thereof and the test sample can be a collection of proteins extracted from tissues or cells, a pool of expressed proteins, combinatorial peptide and/ or 20 chemical libraries, or phage displayed peptides. The tissues or cells from which the test proteins are extracted can originate from any species.

In other methods, a target protein is immobilized and the test population is a collection of unique polypeptides encoded by the extended cDNAs or portions thereof.

To study the interaction of the proteins encoded by the extended cDNAs or portions thereof with drugs, the 25 microdialysis coupled to HPLC method described by Wang et al., Chromatographia, 44, 205-208(1997) or the affinity capillary electrophoresis method described by Busch et al., J. Chromatogr. 777:311-328 (1997), the disclosures of which are incorporated herein by referenc can be used.

The system described in U.S. Patent No. 5,654,150 may also be used to identify molecules which interact with the polypeptides encoded by the extended cDNAs. In this system, pools of extended cDNAs are transcribed and 30 translated in vitro and the reaction products are assayed for interaction with a known polypeptide or antibody.

It will be appreciated by those skilled in the art that the proteins expressed from the extended cDNAs or portions may be assayed for numerous activities in addition to those specifically enumerated above. For example, the expressed proteins may be evaluated for applications involving control and regulation of inflammation, tumor

proliferation or metastasis, infection, or other clinical conditions. In addition, the proteins expressed from the extended cDNAs or portions thereof may be useful as nutritional agents or cosmetic agents.

The proteins expressed from the extended cDNAs or portions thereof may be used to generate antibodies capable of specifically binding to the expressed protein or fragments thereof as described in Example 40 below. The antibodies may capable of binding a full length protein encoded by one of the sequences of SEQ ID NOs. 40-140 and 242-377, or a signal peptide encoded by one of the sequences of SEQ ID Nos. 40-140 and 242-377. Alternatively, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 10 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In some embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 15 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In other embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 25 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513. In further embodiments, the antibodies may be capable of binding fragments of the proteins expressed from the extended cDNAs which comprise at least 40 amino acids of the sequences of SEQ ID NOs: 141-241 and 378-513.

#### **EXAMPLE 40**

#### Production of an Antibody to a Human Protein

Substantially pure protein or polypeptide is isolated from the transfected or transformed cells as described in Example 30. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few micrograms/ml. Monoclonal or polyclonal antibody to the protein can then be prepared as follows:

#### A. Monoclonal Antibody Production by Hybridoma Fusion

Monoclonal antibody to epitopes of any of the peptides identified and isolated as described can be prepared from murine hybridomas according to the classical method of Kohler, G. and Milstein, C., Nature 256:495 (1975) or derivative methods thereof. Briefly, a mouse is repetitively inoculated with a few micrograms of the selected protein or peptides derived therefrom over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as Elisa, as originally described by Engvall, E., Meth. Enzymol. 70:419 (1980), and derivative methods thereof. Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York, Section 21-2.

## B. Polyclonal Antibody Production by Immunization

Polyclonal antiserum containing antibodies to heterogenous epitopes of a single protein can be prepared by immunizing suitable animals with the expressed protein or peptides derived therefrom described above, which can be unmodified or modified to enhance immunogenicity. Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. For example, small molecules tend to be less immunogenic than others and may require the use of carriers and adjuvant. Also, host animals vary in response to site of inoculations and dose, with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971).

Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: **Handbook of Experimental Immunology** D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 µM). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: **Manual of Clinical Immunology**, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

## V. Use of Extended cDNAs or Portions Thereof as Reagents

The extended cDNAs of the present invention may be used as reagents in isolation procedures, diagnostic assays, and forensic procedures. For example, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be detectably labeled and used as probes to isolate other sequences capable of hybridizing to them. In addition, sequences from the extended cDNAs (or genomic DNAs obtainable therefrom) may be used to design PCR primers to be used in isolation, diagnostic, or forensic procedures.

#### **EXAMPLE 41**

## Preparation of PCR Primers and Amplification of DNA

The extended cDNAs (or genomic DNAs obtainable therefrom) may be used to prepare PCR primers for a variety of applications, including isolation procedures for cloning nucleic acids capable of hybridizing to such sequences, diagnostic techniques and forensic techniques. The PCR primers are at least 10 bases, and preferably at least 12, 15, or 17 bases in length. More preferably, the PCR primers are at least 20-30 bases in length. In some embodiments, the PCR primers may be more than 30 bases in length. It is preferred that the primer pairs have approximately the same G/C

ratio, so that melting temperatures are approximately the same. A variety of PCR techniques are familiar to those skilled in the art. For a review of PCR technology, see Molecular Cloning to Genetic Engineering White, B.A. Ed. in Methods in Molecular Biology 67: Humana Press, Totowa 1997. In each of these PCR procedures, PCR primers on either side of the nucleic acid sequences to be amplified are added to a suitably prepared nucleic acid sample along with dNTPs and a thermostable polymerase such as Taq polymerase, Pfu polymerase, or Vent polymerase. The nucleic acid in the sample is denatured and the PCR primers are specifically hybridized to complementary nucleic acid sequences in the sample. The hybridized primers are extended. Thereafter, another cycle of denaturation, hybridization, and extension is initiated. The cycles are repeated multiple times to produce an amplified fragment containing the nucleic acid sequence between the primer sites.

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#### **EXAMPLE 42**

#### Use of Extended cDNAs as Probes

Probes derived from extended cDNAs or portions thereof (or genomic DNAs obtainable therefrom) may be labeled with detectable labels familiar to those skilled in the art, including radioisotopes and non-radioactive labels, to provide a detectable probe. The detectable probe may be single stranded or double stranded and may be made using techniques known in the art, including in vitro transcription, nick translation, or kinase reactions. A nucleic acid sample containing a sequence capable of hybridizing to the labeled probe is contacted with the labeled probe. If the nucleic acid in the sample is double stranded, it may be denatured prior to contacting the probe. In some applications, the nucleic acid sample may be immobilized on a surface such as a nitrocellulose or nylon membrane. The nucleic acid sample may comprise nucleic acids obtained from a variety of sources, including genomic DNA, cDNA libraries, RNA, or tissue samples.

Procedures used to detect the presence of nucleic acids capable of hybridizing to the detectable probe include well known techniques such as Southern blotting, Northern blotting, dot blotting, colony hybridization, and plaque hybridization. In some applications, the nucleic acid capable of hybridizing to the labeled probe may be cloned into vectors such as expression vectors, sequencing vectors, or in vitro transcription vectors to facilitate the characterization and expression of the hybridizing nucleic acids in the sample. For example, such techniques may be used to isolate and clone sequences in a genomic library or cDNA library which are capable of hybridizing to the detectable probe as described in Example 30 above.

PCR primers made as described in Example 41 above may be used in forensic analyses, such as the DNA fingerprinting techniques described in Examples 43-47 below. Such analyses may utilize detectable probes or primers based on the sequences of the extended cDNAs isolated using the 5' ESTs (or genomic DNAs obtainable therefrom).

#### **EXAMPLE 43**

#### Forensic Matching by DNA Sequencing

In one exemplary method, DNA samples are isolated from forensic specimens of, for example, hair, semen, blood or skin cells by conventional methods. A panel of PCR primers based on a number of the extended cDNAs (or

genomic DNAs obtainable therefrom), is then utilized in accordance with Example 41 to amplify DNA of approximately 100-200 bases in length from the forensic specimen. Corresponding sequences are obtained from a test subject. Each of these identification DNAs is then sequenced using standard techniques, and a simple database comparison determines the differences, if any, between the sequences from the subject and those from the sample. Statistically significant differences between the suspect's DNA sequences and those from the sample conclusively prove a lack of identity. This lack of identity can be proven, for example, with only one sequence. Identity, on the other hand, should be demonstrated with a large number of sequences, all matching. Preferably, a minimum of 50 statistically identical sequences of 100 bases in length are used to prove identity between the suspect and the sample.

#### **EXAMPLE 44**

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#### Positive Identification by DNA Sequencing

The technique outlined in the previous example may also be used on a larger scale to provide a unique fingerprint-type identification of any individual. In this technique, primers are prepared from a large number of sequences from Table IV and the appended sequence listing. Preferably, 20 to 50 different primers are used. These primers are used to obtain a corresponding number of PCR-generated DNA segments from the individual in question in accordance with Example 41. Each of these DNA segments is sequenced, using the methods set forth in Example 43. The database of sequences generated through this procedure uniquely identifies the individual from whom the sequences were obtained. The same panel of primers may then be used at any later time to absolutely correlate tissue or other biological specimen with that individual.

#### **EXAMPLE 45**

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#### Southern Blot Forensic Identification

The procedure of Example 44 is repeated to obtain a panel of at least 10 amplified sequences from an individual and a specimen. Preferably, the panel contains at least 50 amplified sequences. More preferably, the panel contains 100 amplified sequences. In some embodiments, the panel contains 200 amplified sequences. This PCR-generated DNA is then digested with one or a combination of, preferably, four base specific restriction enzymes. Such enzymes are commercially available and known to those of skill in the art. After digestion, the resultant gene fragments are size separated in multiple duplicate wells on an agarose gel and transferred to nitrocellulose using Southern blotting techniques well known to those with skill in the art. For a review of Southern blotting see Davis et al. (Basic Methods in Molecular Biology, 1986, Elsevier Press. pp 62-65).

A panel of probes based on the sequences of the extended cDNAs (or genomic DNAs obtainable therefrom), or fragments thereof of at least 10 bases, are radioactively or colorimetrically labeled using methods known in the art, such as nick translation or end labeling, and hybridized to the Southern blot using techniques known in the art (Davis et al., <a href="mailto:supra">supra</a>). Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30

nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 100, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, at least 5 to 10 of these labeled probes are used, and more preferably at least about 20 or 30 are 5 used to provide a unique pattern. The resultant bands appearing from the hybridization of a large sample of extended cDNAs (or genomic DNAs obtainable therefrom) will be a unique identifier. Since the restriction enzyme cleavage will be different for every individual, the band pattern on the Southern blot will also be unique. Increasing the number of extended cDNA probes will provide a statistically higher level of confidence in the identification since there will be an increased number of sets of bands used for identification.

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#### **EXAMPLE 46**

#### **Dot Blot Identification Procedure**

Another technique for identifying individuals using the extended cDNA sequences disclosed herein utilizes a dot blot hybridization technique.

Genomic DNA is isolated from nuclei of subject to be identified. Oligonucleotide probes of approximately 30 bp 15 in length are synthesized that correspond to at least 10, preferably 50 sequences from the extended cDNAs or genomic DNAs obtainable therefrom. The probes are used to hybridize to the genomic DNA through conditions known to those in the art. The oligonucleotides are end labeled with P<sup>32</sup> using polynucleotide kinase (Pharmacia). Dot Blots are created by spotting the genomic DNA onto nitrocellulose or the like using a vacuum dot blot manifold (BioRad, Richmond California). The nitrocellulose filter containing the genomic sequences is baked or UV linked to the filter, prehybridized and 20 hybridized with labeled probe using techniques known in the art (Davis et al. supra). The 32P labeled DNA fragments are sequentially hybridized with successively stringent conditions to detect minimal differences between the 30 bp sequence and the DNA. Tetramethylammonium chloride is useful for identifying clones containing small numbers of nucleotide mismatches (Wood et al., Proc. Natl. Acad. Sci. USA 82(6):1585-1588 (1985)). A unique pattern of dots distinguishes one individual from another individual.

Extended cDNAs or oligonucleotides containing at least 10 consecutive bases from these sequences can be used as probes in the following alternative fingerprinting technique. Preferably, the probe comprises at least 12, 15, or 17 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). More preferably, the probe comprises at least 20-30 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom). In some embodiments, the probe comprises more than 30 nucleotides from the extended cDNA (or genomic 30 DNAs obtainable therefrom). In other embodiments, the probe comprises at least 40, at least 50, at least 75, at least 1DO, at least 150, or at least 200 consecutive nucleotides from the extended cDNA (or genomic DNAs obtainable therefrom).

Preferably, a plurality of probes having sequences from different genes are used in the alternative fingerprinting technique. Example 47 below provides a representative alternative fingerprinting procedure in which the probes are derived from extended cDNAs.

### **EXAMPLE 47**

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# Alternative "Fingerprint" Identification Technique

20-mer oligonucleotides are prepared from a large number, e.g. 5D, 100, or 200, of extended cDNA sequences (or genomic DNAs obtainable therefrom) using commercially available oligonucleotide services such as Genset, Paris, France. Cell samples from the test subject are processed for DNA using techniques well known to those with skill in the art. The nucleic acid is digested with restriction enzymes such as EcoRI and Xbal. Following digestion, samples are applied to wells for electrophoresis. The procedure, as known in the art, may be modified to accommodate polyacrylamide electrophoresis, however in this example, samples containing 5 ug of DNA are loaded into wells and separated on 0.8% agarose gels. The gels are transferred onto nitrocellulose using standard Southern blotting techniques.

10 ng of each of the oligonucleotides are pooled and end-labeled with P<sup>32</sup>. The nitrocellulose is prehybridized with blocking solution and hybridized with the labeled probes. Following hybridization and washing, the nitrocellulose filter is exposed to X-Omat AR X-ray film. The resulting hybridization pattern will be unique for each individual.

It is additionally contemplated within this example that the number of probe sequences used can be varied for additional accuracy or clarity.

The antibodies generated in Examples 30 and 40 above may be used to identify the tissue type or cell species from which a sample is derived as described above.

### **EXAMPLE 48**

# Identification of Tissue Types or Cell Species by Means of

### Labeled Tissue Specific Antibodies

Identification of specific tissues is accomplished by the visualization of tissue specific antigens by means of
antibody preparations according to Examples 30 and 40 which are conjugated, directly or indirectly to a detectable
marker. Selected labeled antibody species bind to their specific antigen binding partner in tissue sections, cell
suspensions, or in extracts of soluble proteins from a tissue sample to provide a pattern for qualitative or semiqualitative interpretation.

Antisera for these procedures must have a potency exceeding that of the native preparation, and for that
reason, antibodies are concentrated to a mg/ml level by isolation of the gamma globulin fraction, for example, by ionexchange chromatography or by ammonium sulfate fractionation. Also, to provide the most specific antisera, unwanted
antibodies, for example to common proteins, must be removed from the gamma globulin fraction, for example by means
of insoluble immunoabsorbents, before the antibodies are labeled with the marker. Either monoclonal or heterologous
antisera is suitable for either procedure.

### A. Immunohistochemical Techniques

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Purified, high-titer antibodies, prepared as described above, are conjugated to a detectable marker, as described, for example, by Fudenberg, H., Chap. 26 in: Basic 503 Clinical Immunology, 3rd Ed. Lange, Los Altos, California (1980) or Rose, N. et al., Chap. 12 in: Methods in Immunodiagnosis, 2d Ed. John Wiley 503 Sons, New York (1980).

A fluorescent marker, either fluorescein or rhodamine, is preferred, but antibodies can also be labeled with an enzyme that supports a color producing reaction with a substrate, such as horseradish peroxidase. Markers can be added to tissue-bound antibody in a second step, as described below. Alternatively, the specific antitissue antibodies can be labeled with ferritin or other electron dense particles, and localization of the ferritin coupled antigen-antibody complexes achieved by means of an electron microscope. In yet another approach, the antibodies are radiolabeled, with, for example <sup>125</sup>I, and detected by overlaying the antibody treated preparation with photographic emulsion.

Preparations to carry out the procedures can comprise monoclonal or polyclonal antibodies to a single protein or peptide identified as specific to a tissue type, for example, brain tissue, or antibody preparations to several antigenically distinct tissue specific antigens can be used in panels, independently or in mixtures, as required.

Tissue sections and cell suspensions are prepared for immunohistochemical examination according to common histological techniques. Multiple cryostat sections (about 4 µm, unfixed) of the unknown tissue and known control, are mounted and each slide covered with different dilutions of the antibody preparation. Sections of known and unknown tissues should also be treated with preparations to provide a positive control, a negative control, for example, pre-immune sera, and a control for non-specific staining, for example, buffer.

Treated sections are incubated in a humid chamber for 30 min at room temperature, rinsed, then washed in buffer for 30-45 min. Excess fluid is blotted away, and the marker developed.

If the tissue specific antibody was not labeled in the first incubation, it can be labeled at this time in a second antibody-antibody reaction, for example, by adding fluorescein- or enzyme-conjugated antibody against the immunoglobulin class of the antiserum-producing species, for example, fluorescein labeled antibody to mouse IgG. Such labeled sera are commercially available.

The antigen found in the tissues by the above procedure can be quantified by measuring the intensity of color or fluorescence on the tissue section, and calibrating that signal using appropriate standards.

### B. Identification of Tissue Specific Soluble Proteins

The visualization of tissue specific proteins and identification of unknown tissues from that procedure is

30 carried out using the labeled antibody reagents and detection strategy as described for immunohistochemistry; however
the sample is prepared according to an electrophoretic technique to distribute the proteins extracted from the tissue in
an orderly array on the basis of molecular weight for detection.

A tissue sample is homogenized using a Virtis apparatus; cell suspensions are disrupted by Dounce homogenization or osmotic lysis, using detergents in either case as required to disrupt cell membranes, as is the practice

in the art. Insoluble cell components such as nuclei, microsomes, and membrane fragments are removed by ultracentrifugation, and the soluble protein-containing fraction concentrated if necessary and reserved for analysis.

A sample of the soluble protein solution is resolved into individual protein species by conventional SDS polyacrylamide electrophoresis as described, for example, by Davis, L. et al., Section 19-2 in: Basic Methods in 5 Molecular Biology (P. Leder, ed), Elsevier, New York (1986), using a range of amounts of polyacrylamide in a set of gels to resolve the entire molecular weight range of proteins to be detected in the sample. A size marker is run in parallel for purposes of estimating molecular weights of the constituent proteins. Sample size for analysis is a convenient volume of from 5 to 55  $\mu$ l, and containing from about 1 to 100  $\mu$ g protein. An aliquot of each of the resolved proteins is transferred by blotting to a nitrocellulose filter paper, a process that maintains the pattern of resolution. Multiple copies 10 are prepared. The procedure, known as Western Blot Analysis, is well described in Davis, L. et al., (above) Section 19-3. One set of nitrocellulose blots is stained with Coomassie Blue dye to visualize the entire set of proteins for comparison with the antibody bound proteins. The remaining nitrocellulose filters are then incubated with a solution of one or more specific antisera to tissue specific proteins prepared as described in Examples 30 and 40. In this procedure, as in procedure A above, appropriate positive and negative sample and reagent controls are run.

In either procedure A or B, a detectable label can be attached to the primary tissue antigen-primary antibody complex according to various strategies and permutations thereof. In a straightforward approach, the primary specific antibody can be labeled; alternatively, the unlabeled complex can be bound by a labeled secondary anti-IgG antibody. In other approaches, either the primary or secondary antibody is conjugated to a biotin molecule, which can, in a subsequent step, bind an avidin conjugated marker. According to yet another strategy, enzyme labeled or radioactive 20 protein A, which has the property of binding to any IgG, is bound in a final step to either the primary or secondary antibody.

The visualization of tissue specific antigen binding at levels above those seen in control tissues to one or more tissue specific antibodies, prepared from the gene sequences identified from extended cDNA sequences, can identify tissues of unknown origin, for example, forensic samples, or differentiated tumor tissue that has metastasized to foreign 25 bodily sites.

In addition to their applications in forensics and identification, extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to their chromosomal locations. Example 49 below describes radiation hybrid (RH) mapping of human chromosomal regions using extended cDNAs. Example 50 below describes a representative procedure for mapping an extended cDNA (or a genomic DNA obtainable therefrom) to its location on a human chromosome. Example 30 51 below describes mapping of extended cDNAs (or genomic DNAs obtainable therefrom) on metaphase chromosomes by Fluorescence In Situ Hybridization (FISH).

### **EXAMPLE 49**

Radiation hybrid mapping of Extended cDNAs to the human genome

Radiation hybrid (RH) mapping is a somatic cell genetic approach that can be used for high resolution mapping of the human genome. In this approach, cell lines containing one or more human chromosomes are lethally irradiated, breaking each chromosome into fragments whose size depends on the radiation dose. These fragments are rescued by fusion with cultured rodent cells, yielding subclones containing different portions of the human genome. This technique 5 is described by Benham et al. (Genomics 4:509-517, 1989) and Cox et al., (Science 250:245-250, 1990). The random and independent nature of the subclones permits efficient mapping of any human genome marker. Human DNA isolated from a panel of 80-100 cell lines provides a mapping reagent for ordering extended cDNAs (or genomic DNAs obtainable therefrom). In this approach, the frequency of breakage between markers is used to measure distance, allowing construction of fine resolution maps as has been done using conventional ESTs (Schuler et al., Science 274:540-546, 10 1996).

RH mapping has been used to generate a high-resolution whole genome radiation hybrid map of human chromosome 17q22-q25.3 across the genes for growth hormone (GH) and thyr idine kinase (TK) (Foster et al., Genomics 33:185-192, 1996), the region surrounding the Gorlin syndrome gene (Obermayr et al., Eur. J. Hum. Genet. 4:242-245, 1996), 60 loci covering the entire short arm of chromosome 12 (Raeymaekers et al., Genomics 29:170-178, 1995), the 15 region of human chromosome 22 containing the neurofibromatosis type 2 locus (Frazer et al., Genomics 14:574-584, 1992) and 13 loci on the long arm of chromosome 5 (Warrington et al., Genomics 11:701-708, 1991).

### **EXAMPLE 50**

# Mapping of Extended cDNAs to Human Chromosomes using PCR techniques

Extended cDNAs (or genomic DNAs obtainable therefrom) may be assigned to human chromosomes using PCR based methodologies. In such approaches, oligonucleotide primer pairs are designed from the extended cDNA sequence (or the sequence of a genomic DNA obtainable therefrom) to minimize the chance of amplifying through an intron. Preferably, the oligonucleotide primers are 18-23 bp in length and are designed for PCR amplification. The creation of PCR primers from known sequences is well known to those with skill in the art. For a review of PCR technology see 25 Erlich, H.A., PCR Technology; Principles and Applications for DNA Amplification. 1992. W.H. Freeman and Co., New York.

The primers are used in polymerase chain reactions (PCR) to amplify templates from total human genomic DNA. PCR conditions are as follows: 60 ng of genomic DNA is used as a template for PCR with 80 ng of each oligonucleotide primer, 0.6 unit of Taq polymerase, and 1 μCu of a <sup>32</sup>P-labeled deoxycytidine triphosphate. The PCR is 30 performed in a microplate thermocycler (Techne) under the following conditions: 30 cycles of 94°C, 1.4 min; 55°C, 2 min; and 72°C, 2 min; with a final extension at 72°C for 10 min. The amplified products are analyzed on a 6% polyacrylamide sequencing gel and visualized by autoradiography. If the length of the resulting PCR product is identical to the distance between the ends of the primer sequences in the extended cDNA from which the primers are derived, then the PCR reaction is repeated with DNA templates from two panels of human-rodent somatic cell hybrids, BIOS

PCRable DNA (BIOS Corporation) and NIGMS Human-Rodent Somatic Cell Hybrid Mapping Panel Number 1 (NIGMS, Camden, NJ).

PCR is used to screen a series of somatic cell hybrid cell lines containing defined sets of human chromosomes for the presence of a given extended cDNA (or genomic DNA obtainable therefrom). DNA is isolated from the somatic hybrids and used as starting templates for PCR reactions using the primer pairs from the extended cDNAs (or genomic DNAs obtainable therefrom). Only those somatic cell hybrids with chromosomes containing the human gene corresponding to the extended cDNA (or genomic DNA obtainable therefrom) will yield an amplified fragment. The extended cDNAs (or genomic DNAs obtainable therefrom) are assigned to a chromosome by analysis of the segregation pattern of PCR products from the somatic hybrid DNA templates. The single human chromosome present in all cell hybrids that give rise to an amplified fragment is the chromosome containing that extended cDNA (or genomic DNA obtainable therefrom). For a review of techniques and analysis of results from somatic cell gene mapping experiments. (See Ledbetter et al., Genomics 6:475-481 (1990).)

Alternatively, the extended cDNAs (or genomic DNAs obtainable therefrom) may be mapped to individual chromosomes using FISH as described in Example 51 below.

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### **EXAMPLE 51**

# Mapping of Extended 5' ESTs to Chromosomes

# Using Fluorescence in situ Hybridization

Fluorescence in situ hybridization allows the extended cDNA (or genomic DNA obtainable therefrom) to be mapped to a particular location on a given chromosome. The chromosomes to be used for fluorescence in situ hybridization techniques may be obtained from a variety of sources including cell cultures, tissues, or whole blood.

In a preferred embodiment, chromosomal localization of an extended cDNA (or genomic DNA obtainable therefrom) is obtained by FISH as described by Cherif et al. (*Proc. Natl. Acad. Sci. U.S.A.*, **87**:6639-6643, 1990).

Metaphase chromosomes are prepared from phytohemagglutinin (PHA)-stimulated blood cell donors. PHA-stimulated lymphocytes from healthy males are cultured for 72 h in RPMI-1640 medium. For synchronization, methotrexate (10 µM) is added for 17 h, followed by addition of 5-bromodeoxyuridine (5-BudR, 0.1 mM) for 6 h. Colcemid (1 µg/ml) is added for the last 15 min before harvesting the cells. Cells are collected, washed in RPMI, incubated with a hypotonic solution of KCI (75 mM) at 37°C for 15 min and fixed in three changes of methanol:acetic acid (3:1). The cell suspension is dropped onto a glass slide and air dried. The extended cDNA (or genomic DNA obtainable therefrom) is labeled with biotin-16 dUTP by nick translation according to the manufacturer's instructions (Bethesda Research Laboratories, Bethesda, MD), purified using a Sephadex G-50 column (Pharmacia, Upssala, Sweden) and precipitated. Just prior to hybridization, the DNA pellet is dissolved in hybridization buffer (50% formamide, 2 X SSC, 10% dextran sulfate, 1 mg/ml sonicated salmon sperm DNA, pH 7) and the probe is denatured at 70°C for 5-10 min.

Slides kept at  $\cdot 20^{\circ}$ C are treated for 1 h at 37°C with RNase A (100  $\mu$ g/ml), rinsed three times in 2 X SSC and dehydrated in an ethanol series. Chromosome preparations are denatured in 70% formamide, 2 X SSC for 2 min at

70°C, then dehydrated at 4°C. The slides are treated with proteinase K (10 μg/100 ml in 20 mM Tris-HCl, 2 mM CaCl<sub>2</sub>) at 37°C for 8 min and dehydrated. The hybridization mixture containing the probe is placed on the slide, covered with a coverslip, sealed with rubber cement and incubated overnight in a humid chamber at 37°C. After hybridization and post-hybridization washes, the biotinylated probe is detected by avidin-FITC and amplified with additional layers of biotinylated goat anti-avidin and avidin-FITC. For chromosomal localization, fluorescent R-bands are obtained as previously described (Cherif et al., *supra*.). The slides are observed under a LEICA fluorescence microscope (DMRXA). Chromosomes are counterstained with propidium iodide and the fluorescent signal of the probe appears as two symmetrical yellow-green spots on both chromatids of the fluorescent R-band chromosome (red). Thus, a particular extended cDNA (or genomic DNA obtainable therefrom) may be localized to a particular cytogenetic R-band on a given chromosome.

Once the extended cDNAs (or genomic DNAs obtainable therefrom) have been assigned to particular chromosomes using the techniques described in Examples 49-51 above, they may be utilized to construct a high resolution map of the chromosomes on which they are located or to identify the chromosomes in a sample.

#### **EXAMPLE 52**

### Use of Extended cDNAs to Construct or Expand Chromosome Maps

Chromosome mapping involves assigning a given unique sequence to a particular chromosome as described above. Once the unique sequence has been mapped to a given chromosome, it is ordered relative to other unique sequences located on the same chromosome. One approach to chromosome mapping utilizes a series of yeast artificial chromosomes (YACs) bearing several thousand long inserts derived from the chromosomes of the organism from which the extended cDNAs (or genomic DNAs obtainable therefrom) are obtained. This approach is described in Ramaiah Nagaraja et al. Genome Research 7:210-222, March 1997. Briefly, in this approach each chromosome is broken into overlapping pieces which are inserted into the YAC vector. The YAC inserts are screened using PCR or other methods to determine whether they include the extended cDNA (or genomic DNA obtainable therefrom) whose position is to be determined. Once an insert has been found which includes the extended cDNA (or genomic DNA obtainable therefrom), the insert can be analyzed by PCR or other methods to determine whether the insert also contains other sequences known to be on the chromosome or in the region from which the extended cDNA (or genomic DNA obtainable therefrom) was derived. This process can be repeated for each insert in the YAC library to determine the location of each of the extended cDNAs (or genomic DNAs obtainable therefrom) relative to one another and to other known chromosomal markers. In this way, a high resolution map of the distribution of numerous unique markers along each of the organisms of the organisms.

As described in Example 53 below extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to identify genes associated with a particular phenotype, such as hereditary disease or drug response.

### **EXAMPLE 53**

Identification of genes associated with hereditary diseases or drug response

This example illustrates an approach useful for the association of extended cDNAs (or genomic DNAs obtainable therefrom) with particular phenotypic characteristics. In this example, a particular extended cDNA (or genomic DNA obtainable therefrom) is used as a test probe to associate that extended cDNA (or genomic DNA obtainable therefrom) with a particular phenotypic characteristic.

Extended cDNAs (or genomic DNAs obtainable therefrom) are mapped to a particular location on a human chromosome using techniques such as those described in Examples 49 and 50 or other techniques known in the art. A search of Mendelian Inheritance in Man (V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) reveals the region of the human chromosome which contains the extended cDNA (or genomic DNA obtainable therefrom) to be a very gene rich region containing several known genes and several 10 diseases or phenotypes for which genes have not been identified. The gene corresponding to this extended cDNA (or genomic DNA obtainable therefrom) thus becomes an immediate candidate for each of these genetic diseases.

Cells from patients with these diseases or phenotypes are isolated and expanded in culture. PCR primers from the extended cDNA (or genomic DNA obtainable therefrom) are used to screen genomic DNA, mRNA or cDNA obtained from the patients. Extended cDNAs (or genomic DNAs obtainable therefrom) that are not amplified in the patients can 15 be positively associated with a particular disease by further analysis. Alternatively, the PCR analysis may yield fragments of different lengths when the samples are derived from an individual having the phenotype associated with the disease than when the sample is derived from a healthy individual, indicating that the gene containing the extended cDNA may be responsible for the genetic disease.

# VI. Use of Extended cDNAs (or genomic DNAs obtainable therefrom) to Construct Vectors

The present extended cDNAs (or genomic DNAs obtainable therefrom) may also be used to construct secretion vectors capable of directing the secretion of the proteins encoded by genes inserted in the vectors. Such secretion vectors may facilitate the purification or enrichment of the proteins encoded by genes inserted therein by reducing the number of background proteins from which the desired protein must be purified or enriched. Exemplary secretion vectors are described in Example 54 below.

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### **EXAMPLE 54**

## Construction of Secretion Vectors

The secretion vectors of the present invention include a promoter capable of directing gene expression in the host cell, tissue, or organism of interest. Such promoters include the Rous Sarcoma Virus promoter, the SV40 promoter, the human cytomegalovirus promoter, and other promoters familiar to those skilled in the art.

A signal sequence from an extended cDNA (or genomic DNA obtainable therefrom), such as one of the signal 30 sequences in SEQ ID NOs: 40-140 and 242-377 as defined in Table IV above, is operably linked to the promoter such that the mRNA transcribed from the promoter will direct the translation of the signal peptide. The host cell, tissue, or organism may be any cell, tissue, or organism which recognizes the signal peptide encoded by the signal sequence in the

extended cDNA (or genomic DNA obtainable therefrom). Suitable hosts include mammalian cells, tissues or organisms, avian cells, tissues, or organisms, insect cells, tissues or organisms, or yeast.

In addition, the secretion vector contains cloning sites for inserting genes encoding the proteins which are to be secreted. The cloning sites facilitate the cloning of the insert gene in frame with the signal sequence such that a fusion 5 protein in which the signal peptide is fused to the protein encoded by the inserted gene is expressed from the mRNA transcribed from the promoter. The signal peptide directs the extracellular secretion of the fusion protein.

The secretion vector may be DNA or RNA and may integrate into the chromosome of the host, be stably maintained as an extrachromosomal replicon in the host, be an artificial chromosome, or be transiently present in the host. Many nucleic acid backbones suitable for use as secretion vectors are known to those skilled in the art, including 10 retroviral vectors, SV40 vectors, Bovine Papilloma Virus vectors, yeast integrating plasmids, yeast episomal plasmids, yeast artificial chromosomes, human artificial chromosomes, P element vectors, baculovirus vectors, or bacterial plasmids capable of being transiently introduced into the host.

The secretion vector may also contain a polyA signal such that the polyA signal is located downstream of the gene inserted into the secretion vector.

After the gene encoding the protein for which secretion is desired is inserted into the secretion vector, the secretion vector is introduced into the host cell, tissue, or organism using calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection, viral particles or as naked DNA. The protein encoded by the inserted gene is then purified or enriched from the supernatant using conventional techniques such as ammonium sulfate precipitation, immunoprecipitation, immunochromatography, size exclusion chromatography, ion exchange 20 chromatography, and hplc. Alternatively, the secreted protein may be in a sufficiently enriched or pure state in the supernatant or growth media of the host to permit it to be used for its intended purpose without further enrichment.

The signal sequences may also be inserted into vectors designed for gene therapy. In such vectors, the signal sequence is operably linked to a promoter such that mRNA transcribed from the promoter encodes the signal peptide. A cloning site is located downstream of the signal sequence such that a gene encoding a protein whose secretion is 25 desired may readily be inserted into the vector and fused to the signal sequence. The vector is introduced into an appropriate host cell. The protein expressed from the promoter is secreted extracellularly, thereby producing a therapeutic effect.

The extended cDNAs or 5' ESTs may also be used to clone sequences located upstream of the extended cDNAs or 5' ESTs which are capable of regulating gene expression, including promoter sequences, enhancer sequences, and 30 other upstream sequences which influence transcription or translation levels. Once identified and cloned, these upstream regulatory sequences may be used in expression vectors designed to direct the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative fashion. Example 55 describes a method for cloning sequences upstream of the extended cDNAs or 5' ESTs.

# Use of Extended cDNAs or 5' ESTs to Clone Upstream

### Sequences from Genomic DNA

Sequences derived from extended cDNAs or 5' ESTs may be used to isolate the promoters of the corresponding genes using chromosome walking techniques. In one chromosome walking technique, which utilizes the GenomeWalker<sup>TM</sup> kit available from Clontech, five complete genomic DNA samples are each digested with a different restriction enzyme which has a 6 base recognition site and leaves a blunt end. Following digestion, oligonucleotide adapters are ligated to each end of the resulting genomic DNA fragments.

For each of the five genomic DNA libraries, a first PCR reaction is performed according to the manufacturer's instructions using an outer adaptor primer provided in the kit and an outer gene specific primer. The gene specific primer should be selected to be specific for the extended cDNA or 5' EST of interest and should have a melting temperature, length, and location in the extended cDNA or 'EST which is consistent with its use in PCR reactions. Each first PCR reaction contains 5ng of genomic DNA, 5  $\mu$ l of 10X Tth reaction buffer, 0.2 mM of each dNTP, 0.2  $\mu$ M each of outer adaptor primer and outer gene specific primer, 1.1 mM of Mg(0Ac)<sub>2</sub>, and 1  $\mu$ l of the Tth polymerase 50X mix in a total volume of 50  $\mu$ l. The reaction cycle for the first PCR reaction is as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (7 cycles) / 2 sec @ 94°C, 3 min @ 67°C (32 cycles) / 5 min @ 67°C.

The product of the first PCR reaction is diluted and used as a template for a second PCR reaction according to the manufacturer's instructions using a pair of nested primers which are located internally on the amplicon resulting from the first PCR reaction. For example, 5  $\mu$ l of the reaction product of the first PCR reaction mixture may be diluted 180 times. Reactions are made in a 50  $\mu$ l volume having a composition identical to that of the first PCR reaction except the nested primers are used. The first nested primer is specific for the adaptor, and is provided with the GenomeWalker<sup>TM</sup> kit. The second nested primer is specific for the particular extended cDNA or 5' EST for which the promoter is to be cloned and should have a melting temperature, length, and location in the extended cDNA or 5' EST which is consistent with its use in PCR reactions. The reaction parameters of the second PCR reaction are as follows: 1 min @ 94°C / 2 sec @ 94°C, 3 min @ 72°C (6 cycles) / 2 sec @ 94°C, 3 min @ 67°C (25 cycles) / 5 min @ 67°C

The product of the second PCR reaction is purified, cloned, and sequenced using standard techniques.

Alternatively, two or more human genomic DNA libraries can be constructed by using two or more restriction enzymes. The digested genomic ONA is cloned into vectors which can be converted into single stranded, circular, or linear DNA. A biotinylated oligonucleotide comprising at least 15 nucleotides from the extended cDNA or 5' EST sequence is hybridized to the single stranded DNA. Hybrids between the biotinylated oligonucleotide and the single stranded DNA containing the extended cONA or EST sequence are isolated as described in Example 29 above. Thereafter, the single stranded DNA containing the extended cDNA or EST sequence is released from the beads and converted into double stranded DNA using a primer specific for the extended cDNA or 5' EST sequence or a primer corresponding to a sequence included in the cloning vector. The resulting double stranded DNA is transformed into bacteria. DNAs containing the 5' EST or extended cONA sequences are identified by colony PCR or colony hybridization.

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Once the upstream genomic sequences have been cloned and sequenced as described above, prospective promoters and transcription start sites within the upstream sequences may be identified by comparing the sequences upstream of the extended cDNAs or 5' ESTs with databases containing known transcription start sites, transcription factor binding sites, or promoter sequences.

In addition, promoters in the upstream sequences may be identified using promoter reporter vectors as described in Example 56.

### **EXAMPLE 56**

### Identification of Promoters in Cloned Upstream Sequences

The genomic sequences upstream of the extended cDNAs or 5' ESTs are cloned into a suitable promoter 10 reporter vector, such as the pSEAP-Basic, pSEAP-Enhancer, p\u00edgal-Basic, p\u00edgal-Enhancer, or pEGFP-1 Promoter Reporter vectors available from Clontech. Briefly, each of these promoter reporter vectors include multiple cloning sites positioned upstream of a reporter gene encoding a readily assayable protein such as secreted alkaline phosphatase, etagalactosidase, or green fluorescent protein. The sequences upstream of the extended cDNAs or 5' ESTs are inserted into the cloning sites upstream of the reporter gene in both orientations and introduced into an appropriate host cell. The 15 level of reporter protein is assayed and compared to the level obtained from a vector which lacks an insert in the cloning site. The presence of an elevated expression level in the vector containing the insert with respect to the control vector indicates the presence of a promoter in the insert. If necessary, the upstream sequences can be cloned into vectors which contain an enhancer for augmenting transcription levels from weak promoter sequences. A significant level of expression above that observed with the vector lacking an insert indicates that a promoter sequence is present in the 20 inserted upstream sequence.

Appropriate host cells for the promoter reporter vectors may be chosen based on the results of the above described determination of expression patterns of the extended cDNAs and ESTs. For example, if the expression pattern analysis indicates that the mRNA corresponding to a particular extended cDNA or 5' EST is expressed in fibroblasts, the promoter reporter vector may be introduced into a human fibroblast cell line.

Promoter sequences within the upstream genomic DNA may be further defined by constructing nested deletions in the upstream DNA using conventional techniques such as Exonuclease III digestion. The resulting deletion fragments can be inserted into the promoter reporter vector to determine whether the deletion has reduced or obliterated promoter activity. In this way, the boundaries of the promoters may be defined. If desired, potential individual regulatory sites within the promoter may be identified using site directed mutagenesis or linker scanning to obliterate 30 potential transcription factor binding sites within the promoter individually or in combination. The effects of these mutations on transcription levels may be determined by inserting the mutations into the cloning sites in the promoter reporter vectors.

### **EXAMPLE 57**

Cloning and Identification of Promoters

Using the method described in Example 55 above with 5' ESTs, sequences upstream of several genes were obtained. Using the primer pairs GGG AAG ATG GAG ATA GTA TTG CCT G (SEQ ID NO:29) and CTG CCA TGT ACA TGA TAG AGA GAT TC (SEQ ID NO:30), the promoter having the internal designation P13H2 (SEQ ID NO:31) was obtained.

Using the primer pairs GTA CCA GGGG ACT GTG ACC ATT GC (SEQ ID NO:32) and CTG TGA CCA TTG CTC CCA AGA GAG (SEQ ID NO:33), the promoter having the internal designation P15B4 (SEQ ID NO:34) was obtained.

Using the primer pairs CTG GGA TGG AAG GCA CGG TA (SEQ ID NO:35) and GAG ACC ACA CAG CTA GAC AA (SEQ ID NO:36), the promoter having the internal designation P29B6 (SEQ ID NO:37) was obtained.

Figure 8 provides a schematic description of the promoters isolated and the way they are assembled with the corresponding 5' tags. The upstream sequences were screened for the presence of motifs resembling transcription factor binding sites or known transcription start sites using the computer program MatInspector release 2.0, August 1996.

Figure 9 describes the transcription factor binding sites present in each of these promoters. The columns labeled matrice provides the name of the MatInspector matrix used. The column labeled position provides the 5' postion of the promoter site. Numeration of the sequence starts from the transcription site as determined by matching the genomic sequence with the 5' EST sequence. The column labeled "orientation" indicates the DNA strand on which the site is found, with the + strand being the coding strand as determined by matching the genomic sequence with the sequence of the 5' EST. The column labeled "score" provides the MatInspector score found for this site. The column labeled "length" provides the length of the site in nucleotides. The column labeled "sequence" provides the sequence of the site found.

The promoters and other regulatory sequences located upstream of the extended cDNAs or 5' ESTs may be used to design expression vectors capable of directing the expression of an inserted gene in a desired spatial, temporal, developmental, or quantitative manner. A promoter capable of directing the desired spatial, temporal, developmental, and quantitative patterns may be selected using the results of the expression analysis described in Example 26 above. For example, if a promoter which confers a high level of expression in muscle is desired, the promoter sequence upstream of an extended cDNA or 5' EST derived from an mRNA which is expressed at a high level in muscle, as determined by the method of Example 26, may be used in the expression vector.

Preferably, the desired promoter is placed near multiple restriction sites to facilitate the cloning of the desired insert downstream of the promoter, such that the promoter is able to drive expression of the inserted gene. The promoter may be inserted in conventional nucleic acid backbones designed for extrachromosomal replication, integration into the host chromosomes or transient expression. Suitable backbones for the present expression vectors include retroviral backbones, backbones from eukaryotic episomes such as SV40 or Bovine Papilloma Virus, backbones from bacterial episomes, or artificial chromosomes.

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Preferably, the expression vectors also include a polyA signal downstream of the multiple restriction sites for directing the polyadenylation of mRNA transcribed from the gene inserted into the expression vector.

Following the identification of promoter sequences using the procedures of Examples 55-57, proteins which interact with the promoter may be identified as described in Example 58 below.

### **EXAMPLE 58**

# Identification of Proteins Which Interact with Promoter Sequences, Upstream Regulatory Sequences, or mRNA

Sequences within the promoter region which are likely to bind transcription factors may be identified by homology to known transcription factor binding sites or through conventional mutagenesis or deletion analyses of reporter plasmids containing the promoter sequence. For example, deletions may be made in a reporter plasmid containing the promoter sequence of interest operably linked to an assayable reporter gene. The reporter plasmids carrying various deletions within the promoter region are transfected into an appropriate host cell and the effects of the deletions on expression levels is assessed. Transcription factor binding sites within the regions in which deletions reduce expression levels may be further localized using site directed mutagenesis, linker scanning analysis, or other techniques familiar to those skilled in the art. Nucleic acids encoding proteins which interact with sequences in the promoter may be identified using one-hybrid systems such as those described in the manual accompanying the Matchmaker One-Hybrid System kit available from Clontech (Catalog No. K1603-1). Briefly, the Matchmaker One-hybrid system is used as follows. The target sequence for which it is desired to identify binding proteins is cloned upstream of a selectable reporter gene and integrated into the yeast genome. Preferably, multiple copies of the target sequences are inserted into the reporter plasmid in tandem.

A library comprised of fusions between cDNAs to be evaluated for the ability to bind to the promoter and the activation domain of a yeast transcription factor, such as GAL4, is transformed into the yeast strain containing the integrated reporter sequence. The yeast are plated on selective media to select cells expressing the selectable marker linked to the promoter sequence. The colonies which grow on the selective media contain genes encoding proteins which bind the target sequence. The inserts in the genes encoding the fusion proteins are further characterized by sequencing. In addition, the inserts may be inserted into expression vectors or in vitro transcription vectors. Binding of the polypeptides encoded by the inserts to the promoter DNA may be confirmed by techniques familiar to those skilled in the art, such as gel shift analysis or DNAse protection analysis.

### VII. Use of Extended cDNAs (or Genomic DNAs Obtainable Therefrom) in Gene Therapy

The present invention also comprises the use of extended cDNAs (or genomic DNAs obtainable therefrom) in gene therapy strategies, including antisense and triple helix strategies as described in Examples 57 and 58 below. In antisense approaches, nucleic acid sequences complementary to an mRNA are hybridized to the mRNA intracellularly, thereby blocking the expression of the protein encoded by the mRNA. The antisense sequences may prevent gene expression through a variety of mechanisms. For example, the antisense sequences may inhibit the ability of ribosomes

to translate the mRNA. Alternatively, the antisense sequences may block transport of the mRNA from the nucleus to the cytoplasm, thereby limiting the amount of mRNA available for translation. Another mechanism through which antisense sequences may inhibit gene expression is by interfering with mRNA splicing. In yet another strategy, the antisense nucleic acid may be incorporated in a ribozyme capable of specifically cleaving the target mRNA.

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### **EXAMPLE 59**

### Preparation and Use of Antisense Oligonucleotides

The antisense nucleic acid molecules to be used in gene therapy may be either DNA or RNA sequences. They may comprise a sequence complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom). The antisense nucleic acids should have a length and melting temperature sufficient to permit formation of an intracellular duplex having sufficient stability to inhibit the expression of the mRNA in the duplex. Strategies for designing antisense nucleic acids suitable for use in gene therapy are disclosed in Green et al., Ann. Rev. Biochem. 55:569-597 (1986) and Izant and Weintraub, Cell 36:1007-1015 (1984).

In some strategies, antisense molecules are obtained from a nucleotide sequence encoding a protein by reversing the orientation of the coding region with respect to a promoter so as to transcribe the opposite strand from that which is normally transcribed in the cell. The antisense molecules may be transcribed using in vitro transcription systems such as those which employ T7 or SP6 polymerase to generate the transcript. Another approach involves transcription of the antisense nucleic acids in vivo by operably linking DNA containing the antisense sequence to a promoter in an expression vector.

Alternatively, oligonucleotides which are complementary to the strand normally transcribed in the cell may be synthesized in vitro. Thus, the antisense nucleic acids are complementary to the corresponding mRNA and are capable of hybridizing to the mRNA to create a duplex. In some embodiments, the antisense sequences may contain modified sugar phosphate backbones to increase stability and make them less sensitive to RNase activity. Examples of modifications suitable for use in antisense strategies are described by Rossi et al., Pharmacol. Ther. 50(2):245-254, (1991).

Various types of antisense oligonucleotides complementary to the sequence of the extended cDNA (or genomic DNA obtainable therefrom) may be used. In one preferred embodiment, stable and semi-stable antisense oligonucleotides described in International Application No. PCT W094/23026 are used. In these molecules, the 3' end or both the 3' and 5' ends are engaged in intramolecular hydrogen bonding between complementary base pairs. These molecules are better able to withstand exonuclease attacks and exhibit increased stability compared to conventional antisense 30 oligonucleotides.

In another preferred embodiment, the antisense oligodeoxynucleotides against herpes simplex virus types 1 and 2 described in International Application No. WO 95/04141.

In yet another preferred embodiment, the covalently cross-linked antisense oligonucleotides described in International Application No. WO 96/31523 are used. These double- or single-stranded oligonucleotides comprise one or

more, respectively, inter- or intra-oligonucleotide covalent cross-linkages, wherein the linkage consists of an amide bond between a primary amine group of one strand and a carboxyl group of the other strand or of the same strand, respectively, the primary amine group being directly substituted in the 2' position of the strand nucleotide monosaccharide ring, and the carboxyl group being carried by an aliphatic spacer group substituted on a nucleotide or nucleotide analog of the other strand or the same strand, respectively.

The antisense oligodeoxynucleotides and oligonucleotides disclosed in International Application No. WO 92/18522 may also be used. These molecules are stable to degradation and contain at least one transcription control recognition sequence which binds to control proteins and are effective as decoys therefor. These molecules may contain "hairpin" structures, "dumbbell" structures, "modified dumbbell" structures, "cross-linked" decoy structures and "loop" structures.

In another preferred embodiment, the cyclic double-stranded oligonucleotides described in European Patent Application No. 0 572 287 A2 are used. These ligated oligonucleotide "dumbbells" contain the binding site for a transcription factor and inhibit expression of the gene under control of the transcription factor by sequestering the factor.

Use of the closed antisense oligonucleotides disclosed in International Application No. W0 92/19732 is also contemplated. Because these molecules have no free ends, they are more resistant to degradation by exonucleases than are conventional oligonucleotides. These oligonucleotides may be multifunctional, interacting with several regions which are not adjacent to the target mRNA.

The appropriate level of antisense nucleic acids required to inhibit gene expression may be determined using in vitro expression analysis. The antisense molecule may be introduced into the cells by diffusion, injection, infection or transfection using procedures known in the art. For example, the antisense nucleic acids can be introduced into the body as a bare or naked oligonucleotide, oligonucleotide encapsulated in lipid, oligonucleotide sequence encapsidated by viral protein, or as an oligonucleotide operably linked to a promoter contained in an expression vector. The expression vector may be any of a variety of expression vectors known in the art, including retroviral or viral vectors, vectors capable of extrachromosomal replication, or integrating vectors. The vectors may be DNA or RNA.

The antisense molecules are introduced onto cell samples at a number of different concentrations preferably between 1x10<sup>-10</sup>M to 1x10<sup>-4</sup>M. Once the minimum concentration that can adequately control gene expression is identified, the optimized dose is translated into a dosage suitable for use in vivo. For example, an inhibiting concentration in culture of 1x10<sup>-7</sup> translates into a dose of approximately 0.6 mg/kg bodyweight. Levels of oligonucleotide approaching 100 mg/kg bodyweight or higher may be possible after testing the toxicity of the oligonucleotide in laboratory animals. It is additionally contemplated that cells from the vertebrate are removed, treated with the antisense oligonucleotide, and reintroduced into the vertebrate.

It is further contemplated that the antisense oligonucleotide sequence is incorporated into a ribozyme sequence to enable the antisense to specifically bind and cleave its target mRNA. For technical applications of ribozyme and antisense oligonucleotides see Rossi et al., *supra*.

In a preferred application of this invention, the polypeptide encoded by the gene is first identified, so that the

effectiveness of antisense inhibition on translation can be monitored using techniques that include but are not limited to
antibody-mediated tests such as RIAs and ELISA, functional assays, or radiolabeling.

The extended cDNAs of the present invention (or genomic DNAs obtainable therefrom) may also be used in gene therapy approaches based on intracellular triple helix formation. Triple helix oligonucleotides are used to inhibit transcription from a genome. They are particularly useful for studying alterations in cell activity as it is associated with a particular gene. The extended cDNAs (or genomic DNAs obtainable therefrom) of the present invention or, more preferably, a portion of those sequences, can be used to inhibit gene expression in individuals having diseases associated with expression of a particular gene. Similarly, a portion of the extended cDNA (or genomic DNA obtainable therefrom) can be used to study the effect of inhibiting transcription of a particular gene within a cell. Traditionally, homopurine sequences were considered the most useful for triple helix strategies. However, homopyrimidine sequences can also inhibit gene expression. Such homopyrimidine oligonucleotides bind to the major groove at homopurine:homopyrimidine sequences. Thus, both types of sequences from the extended cDNA or from the gene corresponding to the extended cDNA are contemplated within the scope of this invention.

### **EXAMPLE 60**

# Preparation and use of Triple Helix Probes

The sequences of the extended cDNAs (or genomic DNAs obtainable therefrom) are scanned to identify 10-mer to 20-mer homopyrimidine or homopurine stretches which could be used in triple-helix based strategies for inhibiting gene expression. Following identification of candidate homopyrimidine or homopurine stretches, their efficiency in inhibiting gene expression is assessed by introducing varying amounts of oligonucleotides containing the candidate sequences into tissue culture cells which normally express the target gene. The oligonucleotides may be prepared on an oligonucleotide synthesizer or they may be purchased commercially from a company specializing in custom oligonucleotide synthesis, such as GENSET, Paris. France.

The oligonucleotides may be introduced into the cells using a variety of methods known to those skilled in the art, including but not limited to calcium phosphate precipitation, DEAE-Dextran, electroporation, liposome-mediated transfection or native uptake.

Treated cells are monitored for altered cell function or reduced gene expression using techniques such as

Northern blotting, RNase protection assays, or PCR based strategies to monitor the transcription levels of the target
gene in cells which have been treated with the oligonucleotide. The cell functions to be monitored are predicted based
upon the homologies of the target gene corresponding to the extended cDNA from which the oligonucleotide was derived
with known gene sequences that have been associated with a particular function. The cell functions can also be

predicted based on the presence of abnormal physiologies within cells derived from individuals with a particular inherited disease, particularly when the extended cDNA is associated with the disease using techniques described in Example 53.

The oligonucleotides which are effective in inhibiting gene expression in tissue culture cells may then be introduced in vivo using the techniques described above and in Example 59 at a dosage calculated based on the in vitro results, as described in Example 59.

In some embodiments, the natural (beta) anomers of the oligonucleotide units can be replaced with alpha anomers to render the oligonucleotide more resistant to nucleases. Further, an intercalating agent such as ethidium bromide, or the like, can be attached to the 3' end of the alpha oligonucleotide to stabilize the triple helix. For information on the generation of oligonucleotides suitable for triple helix formation see Griffin et al. (Science 245:967-10 971 (1989).

### **EXAMPLE 61**

### Use of Extended cDNAs to Express an Encoded Protein in a Host Organism

The extended cDNAs of the present invention may also be used to express an encoded protein in a host organism to produce a beneficial effect. In such procedures, the encoded protein may be transiently expressed in the host organism or stably expressed in the host organism. The encoded protein may have any of the activities described above. The encoded protein may be a protein which the host organism lacks or, alternatively, the encoded protein may augment the existing levels of the protein in the host organism.

A full length extended cDNA encoding the signal peptide and the mature protein, or an extended cDNA encoding only the mature protein is introduced into the host organism. The extended cDNA may be introduced into the host organism using a variety of techniques known to those of skill in the art. For example, the extended cDNA may be injected into the host organism as naked DNA such that the encoded protein is expressed in the host organism, thereby producing a beneficial effect.

Alternatively, the extended cDNA may be cloned into an expression vector downstream of a promoter which is active in the host organism. The expression vector may be any of the expression vectors designed for use in gene therapy, including viral or retroviral vectors.

The expression vector may be directly introduced into the host organism such that the encoded protein is expressed in the host organism to produce a beneficial effect. In another approach, the expression vector may be introduced into cells in vitro. Cells containing the expression vector are thereafter selected and introduced into the host organism, where they express the encoded protein to produce a beneficial effect.

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### **EXAMPLE 62**

# Use Of Signal Peptides Encoded By 5' Ests Or Sequences

Obtained Therefrom To Import Proteins Into Cells

The short core hydrophobic region (h) of signal peptides encoded by the 5'ESTS or extended cDNAs derived from the 5'ESTs of the present invention may also be used as a carrier to import a peptide or a protein of interest, so-

called cargo, into tissue culture cells (Lin et al., J. Biol. Chem., 270: 14225-14258 (1995); Du et al., J. Peptide Res., 51: 235-243 (1998); Rojas et al., Nature Biotech., 16: 370-375 (1998)).

When cell permeable peptides of limited size (approximately up to 25 amino acids) are to be translocated across cell membrane, chemical synthesis may be used in order to add the hiregion to either the C-terminus or the N-terminus to the cargo peptide of interest. Alternatively, when longer peptides or proteins are to be imported into cells, nucleic acids can be genetically engineered, using techniques familiar to those skilled in the art, in order to link the extended cDNA sequence encoding the hiregion to the 5' or the 3' end of a DNA sequence coding for a cargo polypeptide. Such genetically engineered nucleic acids are then translated either *in vitro* or *in vivo* after transfection into appropriate cells, using conventional techniques to produce the resulting cell permeable polypeptide. Suitable hosts cells are then simply incubated with the cell permeable polypeptide which is then translocated across the membrane.

This method may be applied to study diverse intracellular functions and cellular processes. For instance, it has been used to probe functionally relevant domains of intracellular proteins and to examine protein-protein interactions involved in signal transduction pathways (Lin et al., supra; Lin et al., J. Biol. Chem., 271: 5305-5308 (1996); Rojas et al., J. Biol. Chem., 271: 27456-27461 (1996); Liu et al., Proc. Natl. Acad. Sci. USA, 93: 11819-11824 (1996); Rojas et al., Bioch. Biophys. Res. Commun., 234: 675-680 (1997)).

Such techniques may be used in cellular therapy to import proteins producing therapeutic effects. For instance, cells isolated from a patient may be treated with imported therapeutic proteins and then re-introduced into the host organism.

Alternatively, the h region of signal peptides of the present invention could be used in combination with a nuclear localization signal to deliver nucleic acids into cell nucleus. Such oligonucleotides may be antisense oligonucleotides or oligonucleotides designed to form triple helixes, as described in examples 59 and 60 respectively, in order to inhibit processing and maturation of a target cellular RNA.

### **EXAMPLE 63**

# Reassembling & Resequencing of Clones

Full length cDNA clones obtained by the procedure described in Example 27 were double-sequenced. These sequences were assembled and the resulting consensus sequences were then reanalyzed. Open reading frames were reassigned following essentially the same process as the one described in Example 27.

After this reanalysis process a few abnormalities were revealed. The sequences presented in SEQ ID NOs: 47, 73, 79, 89, 91, 96, 126, 128, 134, and 139 are apparently unlikely to be genuine full length cDNAs. These clones are missing a stop codon and are thus more probably 3' truncated cDNA sequences. Similarly, the sequences presented in SEQ ID NOs: 45, 50, 54, 57, 73, 74, 89, 92, 95, 98, 126, 129, 130, 131 and 139 may also not be genuine full length cDNAs based on homology studies with existing protein sequences. Although both of these sequences encode a potential start methionine each could represent a 5' truncated cDNA.

In addition, SEQ ID NO: 115 was found to be an alternatively spliced transcript and the identities of some of the bases in SEQ ID NO: 131 were corrected.

Finally, after the reassignment of open reading frames for the clones, new open reading frames were chosen in some instances. For example, in the case of SEQ ID NOs: 41, 47, 50, 52, 54-56, 58, 59, 61, 74, 75, 79, 84, 89, 91, 92, 96, 98, 103, 105, 106, 126, 129, 131, and 133 the new open reading frames were no longer predicted to contain a signal peptide.

As discussed above, Table IV provides the sequence identification numbers of the extended cDNAs of the present invention, the locations of the full coding sequences in SEQ ID NOs: 40-140 and 242-377 (i.e. the nucleotides encoding both the signal peptide and the mature protein, listed under the heading FCS location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the signal peptides (listed under the heading SigPep Location in Table IV), the locations of the nucleotides in SEQ ID NOs: 40-140 and 242-377 which encode the mature proteins generated by cleavage of the signal peptides (listed under the heading Mature Polypeptide Location in Table IV), the locations in SEQ ID NOs: 40-140 and 242-377 of stop codons (listed under the heading Stop Codon Location in Table IV) the locations in SEQ ID NOs: 40-140 and 242-377 of polyA signals (listed under the heading g PolyA Signal Location in Table IV) and the locations of polyA sites (listed under the heading PolyA Site Location in Table IV).

As discussed above, Table V lists the sequence identification numbers of the polypeptides of SEQ ID NOs: 141-241 and 378-513, the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the full length polypeptide (second column), the locations of the amino acid residues of SEQ ID NOs: 141-241 and 378-513 in the signal peptides (third column), and the locations of the amino acid residues of SEQ ID NOs: 141-241 and 379-513 in the mature polypeptide created by cleaving the signal peptide from the fall length polypeptide (fourth column). In Table V, and in the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1 and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

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### **EXAMPLE 64**

### Functional Analysis of Predicted Protein Sequences

Following double-sequencing, new contigs were assembled for each of the extended cDNAs of the present invention and each was compared to known sequences available at the time of filing. These sequences originate from the following databases: Genbank (release 108 and daily releases up to October, 15, 1998), Genseq (release 32) PIR (release 33) and SwissProt (release 35). The predicted proteins of the present invention matching known proteins were further classified into 3 categories depending on the level of homology.

The first category contains proteins of the present invention exhibiting more than 70% identical amino acid residues on the whole length of the matched protein. They are clearly close homologues which most probably have the same function or a very similar function as the matched protein.

The second category contains proteins of the present invention exhibiting more remote homologies  $\langle 40 \text{ to } 70\% \rangle$  over the whole protein) indicating that the protein of the present inventionmay have functions similar to those of the homologous protein.

The third category contains proteins exhibiting homology (90 to 100%) to a domain of a known protein indicating that the matched protein and the protein of the invention may share similar features.

It should be noted that the numbering of amino acids in the protein sequences discussed in Figures 10 to 15, and Table VIII, the first methionine encountered is designated as amino acid number 1. In the appended sequence listing, the first amino acid of the mature protein resulting from cleavage of the signal peptide is designated as amino acid number 1, and the first amino acid of the signal peptide is designated with the appropriate negative number, in accordance with the regulations governing sequence listings.

In addition all of the corrected amino acid sequences (SEQ ED NOs: 141-241 and 378-513) were scanned for the presence of known protein signatures and motifs. This search was performed against the Prosite 15.0 database, using the Proscan software from the GCG package- Functional signatures and their locations are indicated in Table VIII.

# 15 A) Proteins which are closely related to known proteins

### Protein of SEQ ID NO: 217

The protein of SEQ ID NO: 217 encoded by the extended cDNA SEQ ID NO: 116 isolated from lymphocyte shows complete identity to a human protein TFAR19 that may play a role in apoptosis (Genbank accession number AF014955, SEQ ID NO: 516) as shown by the alignment in figure 10.

Taken together, these data suggest that the protein of SEQ ID NO: 217 may be involved in the control of development and homeostasis. Thus, this protein may be useful in diagnosis and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders, viral infections such as AIDS, neurodegenerative disorders, osteoporosis.

# 25 Proteins of SEQ ID NOs: 174, 175 and 232

The proteins of SEQ ID NOs: 174, 175 and 232 encoded by the extended cDNAs SEQ ID NOs:. 73, 74 and 131 respectively and isolated from lymphocytes shows complete extensive homologies to a human secreted protein (Genseq accession number W36955, SEQ ID NO: 517). As shown by the alignments of figure 11, the amino acid residues are identical to those of the 110 amino acid long matched protein except for positions 51 and 108-110 of the matched protein for the protein of SEQ ID NOs: 174, for positions 48, 94 and 108-110 of the matched protein of SEQ ID NOs:175 and for positions 94, and 108-110 of the matched protein for the protein of SEQ ID NOs: 232. Proteins of SEQ IO NOs: 174 and 232 may represent alternative forms issued from alternative use of polyadenylation signals.

Taken together, these data suggest that the proteins of SEQ ID NOs: 174, 175 and 232 may play a role in cell proliferation and/or differentiation, in immune responses and/or in haematopoeisis. Thus, this protein or part therein,

may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

### 5 Proteins of SEQ ID NO: 231

The protein of SEQ ID NO: 231 encoded by the extended cDNA SEQ ID NO: 130 shows extensive homology with the human E25 protein (Genbank accession number AF038953, SEQ ID NO: 515). As shown by the alignments in figure 12, the amino acid residues are identical except for position 159 in the 263 amino acid long matched sequence. The matched protein might be involved in the development and differentiation of haematopoietic stem/progenitor cells.

10 In addition, it is the human homologue of a murine protein thought to be involved in chondro-osteogenic differentiation and belonging to a novel multigene family of integral membrane proteins (Deleersnijder et al, J. Biol. Chem., 271: 19475-19482 (1996)).

The protein of invention contains two short segments from positions 1 to 21 and from 100 to 120 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). The first transmembrane domains matches exactly those predicted for the murine E25 protein.

Taken together, these data suggest that the protein of SEQ ID NO: 231 may be involved in cellular proliferation and differentiation. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and embryogenesis disorders.

### 20 Protein of SEQ ID NO: 196

The protein of SEQ ID NO: 196 encoded by the extended cDNA SEQ ID NO: 95 shows extensive homology with the human seventransmembrane protein (Genbank accession number Y11395, SEQ ID NO: 518) and its murine homologue (Genbank accession number Y11550). As shown by the alignments in figure 13, the amino acid residues are identical except for position 174 in the 399 amino acid long human matched sequence. The matched protein potentially associated to stomatin may act as a G-protein coupled receptor and is likely to be important for the signal transduction in neurons and haematopoietic cells (Mayer et al, Biochem. Biophys. Acta., 1395: 301-308 (1998)).

Taken together, these data suggest that the protein of SEQ ID NOs: 196 may be involved in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases cardiovascular disorders, hypertension, renal injury and repair and septic shock.

### Protein of SEQ ID NO: 158

The protein of SEQ IO NOs: 158 encoded by the extended cDNA SEQ ID NO: 57 shows homology with the murine subunit 7a of the COP9 complex (Genbank accession number AF071316, SEQ ID NO: 520). As shown by the

alignments in figure 14, the amino acid residues are identical except for positions 90, 172 and 247 in the 275 amino acid long matched sequence. This complex is highly conserved between mammals and higher plants where it has been shown to act as a repressor of photomorphogenesis All the components of the mammalian COP9 complex contain structural features also present in components of the proteasome regulatory complex and the translation initiation complex eIF3 complex, suggesting that the mammalian COP9 complex is an important cellular regulator modulating multiple signaling pathways (Wei et al, Curr. Biol., 8 : 919-922 (1998)).

Taken together, these data suggest that the protein of SEO ID NO: 158 may be involved in cellular signaling, probably as a subunit of the human COP9 complex. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

### Protein of SEQ ID NO: 226

The protein of SEQ ID NO: 226 encoded by the extended cDNA SEQ ID NO: 125 shows homology with the bovine subunit B14.5B of the NADH-ubiquinone oxidureductase complex (Arizmendi et al, FEBS Lett., 313: 80-84 (1992) and Swissprot accession -number Q02827, SEQ ID NO: 514). As shown by the alignments in figure 15, the amino acid residues are identical except for positions 3-4, 6-12, 32-34, 47, 53-55, 67 and 69-74 in the 120 amino acid long matched sequence. This complex is the first of four complexes located in the inner mitochondrial membrane and composing the mitochondrial electron transport chain. Complex I is involved in the dehydrogenation of NAOH and the transportation of electrons to coenzyme Q. It is composed of 7 subunits encoded by the mitochondrial genome and 34 subunits encoded by the nuclear genome. It is also thought to play a role in the regulation of apoptosis and necrosis. Mitochondriocytopathies due to complex I deficiency are frequently encountered and affect tissues with a high energy demand such as brain (mental retardation, convulsions, movement disorders), heart (cardiomyopathy, conduction disorders), kidney (Fanconi syndrome), skeletal muscle (exercise intolerance, muscle weakness, hypotonia) and/or eye (opthmaloplegia, ptosis, cataract and retinopathy). For a review on complex I see Smeitink et al., Hum. Mol. Gent., 7: 1573-1579 (1998).

Taken together, these data suggest that the protein of SEQ ID NO: 226 may be part of the mitochondrial energy-generating system, probably as a subunit of the NADH-ubiquinone oxidoreductase complex. Thus, this protein or part therein, may be useful in diagnosing and/or treating several disorders including, but not limited to, brain disorders (mental retardation, convulsions, movement disorders), 'heart disorders (cardiomyopathy, conduction disorders), kidney disorders (Fanconi syndrome), skeletal muscle disorders (exercise intolerance, muscle weakness, hypotonia) and/or eye disorders opthmalmoplegia, ptosis, cataract and retinopathy).

B) Proteins which are remotely related to proteins with known functions

Proteins of SEO ID NOs: 149, 150 and 211

The proteins of SEQ ID NOs: 1.49,150 and 211 encoded by the extended cDNAs SEQ ID NOs: 48, 49 and 110 respectively and found in, skeletal muscle shows homologies with T1/ST2 ligand polypeptide of either human (Genbank accession number U41804 and Genseq accession number W09639) or rodent species (Genbank accession number U41805 and Genseq accession number W09640). These polypeptides are thought to be cytokines that bind to the ST2 receptor, a member of the immunoglobulin family homologous to the interleukin-1 receptor and present on some lymphoma cells. They are predicted to be cell-surface proteins containing a short transmembrane domain. (Gayle et al, J. Biol. Chem., 271: 5784-5789 (1996)). Proteins of SEQ ID NOs: 149, 150 and 211 may represent alternative forms issued from alternative use of polyadenylation signals.

The protein of invention contains two short transmembrane segments from positions 5 to 25 and from 195 to 215 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, **10**:685-686 (1994)). The second transmembrane domain matches exactly those of the matched cell-surface protein.

Taken together, these data suggest that the protein of SEQ ID NOs: 149, 150 and 211 may act as a cytokine, thus may play a role in the regulation of cell growth and differentiation and/or in the regulation of the immune response.

Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents such as HIV and/or to suppress graft rejection.

### Protein of SEQ ID NO: 177

The protein SEQ ID NO: 177 found in testis encoded by the extended cDNA SEQ ID NO: 76 shows homologies to serine protease inhibitor proteins belonging to the pancreatic trypsin inhibitor family (Kunitz) such as the extracellular proteinase inhibitor named chelonianin (Swissprot accession number P00993). The characteristic PROSITE signature of this family is conserved in the protein of the invention (positions 69 to 87) except for a drastic change of the last cysteine residue into an arginine residue.

Taken together, these data suggest that the protein of SEQ ID NO: 177 may be a protease inhibitor, probably of the Kunitz family. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including but not limited to, cancer and neurodegenerative disorders such as Alzheimer's disease.

### Protein of SEQ ID NO: 146

The protein SEQ ID NO: 146 encoded by the extended cDNA SEQ ID NO: 45 shows homology to human apolipoprotein L (Genbank accession number AF019225). The matched protein is a secreted high density lipoprotein associated with apoA-l-containing lipoproteins which play a key role in reverse cholesterol transport.

Taken together, these data suggest that the protein of SEQ ID NO. 146 may play a role in lipid metabolism. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,

hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as, coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia.

### Protein of SEQ ID NO: 163

The protein SEQ ED NO: 163 encoded by the extended cDNA SEQ ID NO: 62 shows homology to the yeast autophagocytosis protein AUT1 (SwissProt accession number P40344). The matched protein is required for starvation-induced non-specific bulk transport of cytoplasmic proteins to the vacuole.

Taken together, these data suggest that the protein of SEQ ID NO: 163 may play a role in protein transport.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to,
autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

# C) Proteins homologous to a domain of a protein with known function

### Protein of SEQ ID NO: 214

The protein of SEQ ID NO: 214 encoded by the extended cDNA SEQ ID NO: 113 and expressed in adult brain shows extensive homology to part of the murine SHYC protein (Genbank accession number AF072697) which is expressed in the developing and embryonic nervous system as well as along the olfactory pathway in adult brains (Köster et al., Neuroscience Letters., 252: 69-71 (1998)).

Taken together, these data suggest that the protein of SEQ ID NO: 214 may play a role in nervous system development and function. Thus, this protein may be useful in diagnosing and/or treating cancer and/or brain disorders, including neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

### Protein of SEQ ID NO: 225

The protein of SEQ ID NO: 225 encoded by the extended cDNA SEQ ID NO: 124 and expressed in adult prostate belong to the phosphatidylethanolainin-binding protein from which it exhibits the characteristic PROSITE signature from positions 90 to 112 (see table VIII). Proteins from this widespread family, from nematodes to fly, yeast, rodent and primate species, bind hydrophobic ligands such as phospholipids and nucleotides. They are mostly expressed in brain and in testis and are thought to play a role in cell growth and/or maturation, in regulation of the sperm maturation, motility and 'in membrane remodeling. They may act either through signal transduction or through oxidoreduction reactions (for a review see Schoentgen and Jollès, *FEBS Letters*, **369**: 22-26 (1995)).

Taken together, these data suggest that the protein of SEQ ID NO: 225 may play a role in cell. Thus, these growth, maturation and in membrane remodeling and/or may be related to male fertility. Thus, this protein may be useful in diagnosing and/or treating cancer, neurodegenerative diseases, and/of, disorders related to male fertility and sterility.

### Protein of SEQ ID NO: 153

The protein of SEQ ID NO: 153 encoded by the extended cDNA SEQ ID NO. 52 and expressed in brain exhibits homology to different integral membrane proteins. These membrane proteins include the nematode protein SRE-2 (Swissprot accession number Q09273) that belongs to the multigene SRE family of *C. elegans* receptor-like proteins and a family of tricarboxylate carriers conserved between flies and mammals. One member of this matched family is the rat tricarboxylate carrier (Genbank accession number S70011), an anion transporter localized in the inner membrane of mitochondria and involved in the biosynthesis of fatty acids and cholesterol. The protein of the invention contains a short transmembrane segments from positions 5 to 25 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10:685-686 (1994)).

Taken together, these data suggest that the protein of SEQ ID NO: 153 may play a role in signal transduction and/or in molecule transport. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, immune disorders, cardiovascular disorders, hypertension, renal injury and repair and septic shock

### Protein of SEQ ID NO: 213

The protein of SEQ ID NO: 213 encoded by the extended cDNA SEQ ID NO: 112 and expressed in brain exhibits homology with part of the tRNA pseudouridine 55 synthase found in *Escherichia Coli* (Swissprot accession number P09171). This bacterial protein belongs to the NAP57/CBF5/TRUB family of nucleolar proteins found in bacteria, yeasts and mammals involved in rRNA or tRNA biosynthesis, ribosomal subunit assembly and/or centromere/mircotubule binding.

Taken together, these data suggest that the protein of SEQ ID NO: 213 may play a role in rRNA or tRNA biogensis and function. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, hearing loss or disorders linked to chromosomal instability such as dyskeratosis.

### Protein of SEQ ED NO: 240

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The protein of SEQ ID NO: 240 encoded by the extended cDNA SEQ ID NO: 139 and expressed in brain exhibits homology with a family of eukaryotic cell surface antigens containing 4 transmembrane domains. The PROSITE signature for this family is conserved in the protein of the invention except for a substitution of an alanine residue in place of any of the following hydrophic residues: leucine, valine, isoleucine or methionine (positions 21 to 36).

The protein of the invention contains three short transmembrane segments from positions 6 to 26, 32 to 52 and from 56 to 76 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). These transmembrane domains match the last three transmembrane domains of the matched protein family.

Taken together, these data suggest that the protein of SEQ IO NO: 240 may play a role in immunological and/or inflammatory responses, probably as a cell surface antigen. Thus, this protein or part therein, may be useful in diagnosing and treating several disorders including, but not limited to, cancer, immunological, haematological and/or

inflammatory disorders. It may also be useful in modulating the immune and inflammatory responses to infectious agents and/or to suppress graft rejection.

### Protein of SEQ ID NO: 239

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The protein of SEQ ID NO: 239 encoded by the extended cDNA SEQ ID NO: 138 exhibits homology with a conserved region in a family of NA+/H+ exchanger conserved in yeast, nematode and mammals. These cation/proton exchangers are integral membrane proteins with 5 transmembrane segments involved in intracellular pH regulation, maintenance of cell volume, reabsorption of sodium across specialized epithelia, vectorial transport and are also thought to play a role in signal transduction and especially in the induction of cell proliferation and in the induction of apoptosis.

The protein of invention contains four short transmembrane segments from positions 21 to 41, 48 to 68 and from 131 to 151 as predicted by the software TopPred II (Claros and von Heijne, *CABIOS applic. Notes*, 10: 685-686 (1994)). The third and fourth transmembrane domains match the fourth and fifth transmembrane segments of the matched family of proteins.

Taken together, these data suggest that the protein of SEQ ID NO: 239 may play a role in membrane

permeability and/or in signal transduction. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair, septic shock as well as disorders of membrane permeability such as diarrhea.

### Protein of SEQ ID NO: 200

The protein of SEQ ID NO: 200 encoded by the extended cDNA SEQ ED NO: 99 and expressed in brain exhibits extensive homology to the N-terminus of cell division cycle protein 23 (Genbank accession number AF053977) and also to a lesser extent to its homologue in Saccharomyces cerevisiae. The matched protein is required for chromosome segregation and is part of the anaphae-promoting complex necessary for cell cycle progression to mitosis.

Taken together, these data suggest that the protein of SEQ ID NO: 200 may play a role in cellular mitosis.

Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer and leukemia.

### Protein of SEQ ID NO: 230

The protein of SEQ ID NO: 230 encoded by the extended cDNA SEQ ID NO: 129 exhibits extensive homology to the C-terminus of the eta subunit of T-complex polypeptide 1 conserved from yeasts to mammals, and even complete identity with the last 54 amino acid residues of the human protein (Genbank accession number AF026292). The matched protein is a chaperonin which assists the folding of actins and tubulins in eukaryotic cells upon ATP hydrolysis.

Taken together, these data suggest that the protein of SEQ ID NO: 230 may play a role in the folding, transport, assembly and degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several

types of disorders including, but not limited to, cancer, cardiovascular disorders, immune disorders, neurodegenerative disorders, osteoporosis and arthritis.

### Protein of SEQ ED NO: 167

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The protein of SEQ ID NO: 167 encoded by the extended cDNA SEQ ID NO: 66 exhibits homology to a monkey pepsinogen A-4 precursor (Swissprot accession number P27678) and to related members of the aspartyl protease family. The matched protein belongs to a family of widely distributed proteolytic enzymes known to exist in vertebrate, fungi, plants, retroviruses and some plant viruses.

Taken together, these data suggest that the protein of SEO ID NO: 167 may play a role in the degradation of proteins. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, autoimmune disorders and immune disorders due to dysfunction of antigen presentation.

### Protein of SEO ID NO: 179

The protein of SEQ ID NO: 179 encoded by the extended cDNA SEQ ID NO: 78 found in testis exhibits

homology to part of mammalian colipase precursors. Colipases are secreted cofactors for pancreatic lipases that allow the lipase to anchor at the water-lipid interface. Colipase plays a crucial role in the intestinal digestion and absorption of dietary fats. The 5 cysteines characteristic for this protein family are conserved in the protein of the invention although the colipase PROSITE signature is not.

Taken together, these data suggest that the protein of SEQ ED NO: 179 may play a role in the lipid metabolism and/or in male fertility. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, hyperlipidemia, hypercholesterolemia, atherosclerosis, cardiovascular disorders such as coronary heart disease, and neurodegenerative disorders such as Alzheimer's disease or dementia, and disorders linked to male fertility.

### 25 Protein of SEO ID NO: 227

The protein of SEQ ID NO: 227 encoded by the extended cDNA SEQ ID NO: 126 exhibits extensive homology to the ATP binding region of a whole family of serine/threonine protein kinases belonging to the CDC2/CDC28 subfamily. The PROSITE signature characteristic for this domain is present in the protein of the invention from positions 10 to 34.

Taken together, these data suggest that the protein of SEQ ED NO: 158 may bind ATP, and even be a protein 30 kinase. Thus, this protein may be useful in diagnosing and/or treating several types of disorders including, but not limited to, cancer, neurodegenerative diseases, cardiovascular disorders, hypertension, renal injury and repair and septic shock.

Although this invention has been described in terms of certain preferred embodiments, other embodiments which will be apparent to those of ordinary skill in the art in view of the disclosure herein are also within the scope of this invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

As discussed above, the extended cDNAs of the present invention or portions thereof can be used for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to 10 compare with endogenous ONA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related ONA sequences; as a source of information to derive PCR primers for genetic fingerprinting; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination for expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or 15 potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins or polypeptides provided by the present invention can similarly be used in assays to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit 20 another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other 25 protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing 30 such methods include without limitation "Molecular Cloning; A Laboratory Manual", 2d ed., Cole Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology; Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a

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nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

# SEQUENCE LISTING FREE TEXT

The following free text appears in the accompanying Sequence Listing: In vitro transcription product oligonucleotide

5 promoter transcription start site Von Heijne matrix Score

matinspector prediction

10 name

TABLE I

SEQ ID NO. in Present application	Provisional Application Disclosing Sequence	SEQ ID NO. in provisional application
40	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	51
41	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	72
42	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	52
43	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	78
44	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	73
45	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	41
46	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	67
47	U.S. Provisional Patent Application Serial No. 60/069,957, filed Oec. 17, 1997	82
48	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	80
49	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	81
50	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	53
51	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	54
52	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	195
53	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	44
54	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	46
55	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	68
56	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	48
57	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	55
58	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	49
59	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	50
60	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	97
61	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	51
62	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	69
63	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	49
64	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	199
65	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	53
66	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	57
67	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	54
68	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	55
69	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	58
70	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	59

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CONT. TABLE I		es.
71	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	60
72	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	112
73	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	52
74	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	59
75	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	60
76	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	136
77	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	75
78	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	61
79	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	61
80	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	130
81	U.S. Provisional Patent Application Serial No. 60/096,116, filed Aug. 10, 1998	65
82	U.S. Provisional Patent Application Serial No. 60/069,957, filed Dec. 17, 1997	54
83	U.S. Provisional Patent Application Serial No. 60/081,563, filed Apr. 13, 1998	78
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85	U.S. Provisional Patent Application Serial No. 60/074,121, filed Feb. 9, 1998	65
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115	U.S. Provisional Patent Application Serial No. 60/066,677, filed Nov. 13, 1997	53
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TABLE II: Parameters used for each step of EST analysis

		Search Charac	teristics	Selection Charac	teristics
Step	Program	Strand	Parameters	Identity (%))	Length (bp)
Miscellaneous	Blastn	both	S=61 X=16	90	17
tRNA	Fasta	both		80	60
rRNA	Blastn	both	S-108	80	40
mtRNA	Blastn	both	S-108	80	40
Procaryotic	Blastn	both	S-144	90	40
Fungal	Blastn	both	S=144	90	40
Alu	fasta*	both	•	70	40
L1	Blastn	both	S=72	70_	40
Repeats	Blastn	both	S=72	70	40
Promoters	Blastn	top	S-54 X-16	90	15⊥
Vertebrate	fasta*	both	S=108	90	30
ESTs	Blatsn	both	S=108 X=16	90	30
Proteins	blastxŋ	top	E = 0.001		,

<sup>\*</sup> use "Quick Fast" Database Scanner

 $<sup>\</sup>perp$  alignment further constrained to begin closer than 10bp to EST\5' end

<sup>5</sup> η using BLOSUM62 substitution matrix

TABLE III: Parameters used for each step of extended cDNA analysis

	Search characte	eristics		Selection	n characteristi	rs .
Step	Program	Strand	Parameters	Identity (%)	Length (bp)	Comments
miscellaneous •	FASTA	both	·	90	15	Comments
tRNA <sup>5</sup>	FASTA	both	Ţ <u>.</u>	80	90	
rRNA*	BLASTN	both	S=108	80	40	+
mtRNA*	BLASTN	both	S=108	80	40	
Procaryotic*	BLASTN	both	S=144	90	40	
Fungai*	BLASTN	both	S=144	90	40	<del> </del>
Alu*	BLASTN	both	S=72	70	40	may 5 matches marking
L1*	BLASTN	both	S-72	70	40	max 5 matches, masking max 5 matches, masking
Repeats*	BLASTN	both	S=72	70	40	masking
PolyA	BLAST2N	top	W-6,S-10,E-1000	90	8	in the last 20 nucleotides
Polyadenylati on signal		top	AATAAA allowing 1 mis	match	1	in the 50 nucleotides preceding the 5' end of the
Vertebrate*	BLASTN then FASTA	both		90 then 70	30	first BLASTN and then FASTA on matching
STs*	BLAST2N	both		90	30	sequences
Geneseq	BLASTN	both	W-8, B-10	90	30	<del> </del>
DRF	BLASTP	top	W-8, B-10			on ORF proteins, max 10
roteins*	BLASTX	top	E-0.001	70	30	1175.101703

steps common to EST analysis and using the same algorithms and parameters
 steps also used in EST analysis but with different algorithms and/or parameters

TABLE IV

ld	FCS Location	SigPep Location	Mature Polypeptide Location	Stop Codon Location	PolyA Signal Location	PolyA Site Location
40	7 through 471	7 through 99	100 through 471	472	537 through 542	554 through 568
41	168 through 332		168 through 332	333	557 through 562	
42	51 through 251	51 through 110	111 through 251	252	849 through 854	882 through 895
43	20 through 613	20 through 82	83 through 613	614		, and again out
44	12 through 416	12 through 86	87 through 416	417	425 through 430	445 through 458
45	276 through 1040	276 through 485	486 through 1040	1041		2024 through 2036
46	443 through 619	443 through 589	590 through 619	620		1267 through 1276
47	206 through 747	1.	206 through 747			
48	36 through 521	36 through 104	105 through 521	522	528 through 533	548 through 561
49	36 through 395	36 through 104	105 through 395	396	599 through 604	619 through 632
50	21 through 41	1.	21 through 41	42	328 through 333	357 through 370
51	35 through 631	35 through 160	161 through 631	632	901 through 906	979 through 994
52	271 through 399		271 through 399	400	,	- Cro timough 004
53	103 through 252	103 through 213	214 through 252	253		588 through 597
54	2 through 460		2 through 460	461	713 through 718	735 through 748
55	31 through 231		31 through 231	232	769 through 774	690 through 703
56	305 through 565		305 through 565	566	694 through 699	713 through 725
57	124 through 873	124 through 378	379 through 873	874	1673 through 1678	1694 through 1705
58	135 through 206	1.	135 through 206	207	850 through 855	1056 through 1069
59	135 through 818		135 through 818	819	909 through 914	1071 through 1084
60	33 through 290	33 through 92	93 through 290	291	· ·	
61	485 through 616		485 through 616	617		669 through 682
62	54 through 995	54 through 227	228 through 995	996	1130 through 1135	1181 through 1191
63	657 through 923	657 through 896	897 through 923	924	957 through 962	974 through 1008
64	18 through 311	18 through 62	63 through 311	312		
65	151 through 426	151 through 258	259 through 426	427	505 through 510	527 through 538
66	10 through 1062	10 through 57	58 through 1062	1063	1710 through 1715	1735 through 1747
67	78 through 491	78 through 218	219 through 491	492	1652 through 1657	1673 through 1686
68	69 through 371	69 through 287	288 through 371	372	510 through 515	530 through 542
69	2 through 757	2 through 205	206 through 757	758		1160 through 1174
70	2 through 1051	2 through 205	206 through 1051	1052	1248 through 1253	1272 through 1285
71	2 through 1171	2 through 205	206 through 1171	1172	1368 through 1373	1386 through 1398
72	42 through 611	42 through 287	288 through 611	612	787 through 792	808 through 821
73	62 through 916	62 through 757	758 through 916			904 through 916
74	62 through 520		62 through 520	521	1124 through 1129	1141 through 1153
75	21 through 167		21 through 167	168		. (4) (INDUGII 1155
76	22 through 318	22 through 93	94 through 318		497 through 502	516 through 526
77	8 through 292	8 through 118	119 through 292		317 through 322	339 through 352
78	16 through 378	16 through 84	85 through 378		502 through 507	522 through 542

CO	NT. TABLE IV					
79	57 through 233		57 through 233	,		
80	83 through 340	83 through 124	125 through 340	341	573 through 578	607 through 660
81	47 through 541	47 through 220	221 through 541	542		597 through 605
82	46 through 285	46 through 150	151 through 285	286	364 through 369	385 through 396
83	22 through 240	22 through 84	85 through 240	241	397 through 402	421 through 432
84	89 through 382		89 through 382	383		408 through 420
85	80 through 415	80 through 142	143 through 415	416	471 through 476	488 through 501
86	152 through 361	152 through 283	284 through 361	362		
87	32 through 307	32 through 70	71 through 307	308	1240 through 1245	1261 through 1272
88	114 through 734	114 through 239	240 through 734	735	768 through 773	793 through 804
89	199 through 802		199 through 802	·	780 through 785	791 through 802
90	38 through 1174	38 through 148	149 through 1174	1175	1452 through 1457	1478 through 1490
91	26 through 361		26 through 361	1.	-	350 through 361
92	3 through 131		3 through 131	132		591 through 605
93	33 through 185	33 through 80	81 through 185	186	570 through 575	586 through 591
94	184 through 915	184 through 237	238 through 915	916	1119 through 1124	1139 through 1150
95	58 through 1116	58 through 159	160 through 1116	1117	1486 through 1491	1504 through 1513
96	327 through 417		327 through 417	-	1.	404 through 417
97	63 through 398	63 through 206	207 through 398	399		
98	2 through 163	,	2 through 163	164	488 through 493	511 through 522
99	13 through 465	13 through 75	76 through 465	466		
100	20 through 703	20 through 94	95 through 703	704	1000 through 1005	1023 through 1041
101	103 through 294	103 through 243	244 through 294	295		
102	81 through 518	81 through 173	174 through 518	519		
103	66 through 326		66 through 326	327	1066 through 1071	1087 through 1098
104	170 through 289	170 through 250	251 through 289	290		
105	36 through 497		36 through 497	498	650 through 655	663 through 685
106	18 through 320		18 through 320	321	539 through 544	542 through 554
107	71 through 1438	71 through 136	137 through 1438	1439	1644 through 1649	1665 through 1678
108	25 through 318	25 through 75	76 through 318	319	452 through 457	482 through 494
109	84 through 332	84 through 170	171 through 332	333		702 through 714
110	32 through 718	32 through 100	101 through 718	719	770 through 775	793 through 805
111	26 through 481	26 through 88	89 through 481	482	755 through 760	775 through 787
112	26 through 562	26 through 187	188 through 562	563	1.	
113	4 through 810	4 through 279	280 through 810	811	858 through 863	881 through 893
114	55 through 459	55 through 120	121 through 459	460	1444 through 1449	1462 through 1475
115	48 through 248	48 through 161	162 through 248	249	283 through 288	308 through 321
116	25 through 399	25 through 186	187 through 399	400		
117	10 through 1137	10 through 72	73 through 1137	1138	1144 through 1149	1162 through 1173
118	72 through 704	72 through 161	162 through 704	705	772 through 777	-
119	44 through 505	44 through 223	224 through 505	506		
120	25 through 393	25 through 150	151 through 393	394	734 through 739	757 through 770

CONT. TABLE IV

CON	IT. TABLE IV					
121	58 through 1095	58 through 114	115 through 1095	1096		1202 through 1213
122	31 through 660	31 through 90	91 through 660	661	1288 through 1293	1307 through 1318
123	31 through 582	31 through 90	91 through 582	583	816 through 821	840 through 853
124	15 through 695	15 through 80	81 through 695	696	795 through 800	814 through 826
125	74 through 295	74 through 196	197 through 295	296	545 through 550	561 through 571
126	440 through 659		440 through 659		601 through 606	
127	38 through 283	38 through 85	86 through 283	284	257 through 262	
128	121 through 477	121 through 288	289 through 477		1.	
129	2 through 163		2 through 163	164	292 through 297	310 through 323
130	46 through 675	46 through 87	88 through 675	676	1364 through 1369	1383 through 1392
131	62 through 385		62 through 385	386	974 through 979	987 through 999
132	422 through 550	422 through 475	476 through 550	551	•	714 through 725
133	124 through 231	·	124 through 231	232		387 through 400
134	131 through 1053	131 through 169	170 through 1053		1019 through 1024	† <del>.</del>
135	86 through 403	86 through 181	182 through 403	404	1097 through 1102	1117 through 1128
136	37 through 162	37 through 93	94 through 162	163	224 through 229 .	243 through 254
137	31 through 381	31 through 90	91 through 381	382		875 through 886
138	46 through 579	46 through 156	157 through 579	580		
139	92 through 471	92 through 172	173 through 471	-	454 through 459	458 through 471
140	154 through 675	154 through 498	499 through 675	676	819 through 824	338 through 849
242	18 through 173	18 through 77	78 through 173	174	864 through 869	882 through 893
243	17 through 595	17 through 85	86 through 595	596	820 through 825	840 through 851
244	89 through 334	89 through 130	131 through 334	335	462 through 467	484 through 495
245	21 through 614	21 through 83	84 through 614	615	849 through 854	873 through 884
246	94 through 573	94 through 258	259 through 573	574	862 through 867	886 through 897
247	74 through 397	74 through 127	128 through 397	398	472 through 477	507 through 518
248	51 through 242	51 through 116	117 through 242	243	319 through 324	339 through 350
249	111 through 191	111 through 155	156 through 191	192	965 through 970	986 through 996
250	45 through 602	45 through 107	108 through 602	603	828 through 833	850 through 860
251	24 through 560	24 through 101	102 through 560	561	563 through 568	583 through 593
252	109 through 558	109 through 273	274 through 558	559	-	1104 through 1114
253	128 through 835	128 through 220	221 through 835	836	1145 through 1150	1170 through 1181
254	59 through 505	59 through 358	359 through 505	506	1042 through 1047	1062 through 1073
255	1 through 207	1 through 147	148 through 207	208	784 through 789	807 through 818
256	12 through 734	12 through 101	102 through 734	.735	914 through 919	961 through 971
257	378 through 518	378 through 467	468 through 518	519	607 through 612	628 through 640
258	110 through 304	110 through 193	194 through 304	305	708 through 713	732 through 743
259	201 through 419	201 through 272	273 through 419	420	601 through 606	627 through 637
260	123 through 302	123 through 176	177 through 302	303	1279 through 1284	1301 through 1312
261	98 through 673	98 through 376	377 through 673	674		1025 through 1035
262	17 through 463	17 through 232	233 through 463	464	657 through 662	684 through 696
263	263 through 481	263 through 322	323 through 481	482		858 through 868
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26	<u>-</u>	42 through 101	102 through 299	300		762 through 775
26		198 through 260	261 through 431	432		1064 through 107
26		279 through 362	363 through 473	474	944 through 949	970 through 981
26	7 12 through 644	12 through 92	93 through 644	645	1002 through 1007	1020 through 103
26	8 91 through 459	91 through 330	331 through 459	460		1271 through 128
269	9 70 through 327	70 through 147	148 through 327	328	1741 through 1746	1763 through 1774
270	12 through 497	12 through 104	105 through 497	498	935 through 940	955 through 967
271	90 through 383	90 through 200	201 through 383	384	609 through 614	632 through 643
272	332 through 541	332 through 376	377 through 541	542	739 through 744	761 through 773
273	43 through 222	43 through 177	178 through 222	223	530 through 535	555 through 566
274	115 through 231	115 through 180	181 through 231	232	419 through 424	445 through 455
275	232 through 384	232 through 300	301 through 384	385	650 through 655	662 through 673
276	143 through 427	143 through 286	287 through 427	428	606 through 611	628 through 639
277	284 through 463	294 through 379	380 through 463	464		762 through 772
278	162 through 671	162 through 398	399 through 671	672	805 through 810	830 through 840
279	63 through 632	63 through 308	309 through 632	633	808 through 813	829 through 840
280	21 through 362	21 through 200	201 through 362	363	821 through 826	838 through 849
281	21 through 503	21 through 344	345 through 503	504	1305 through 1310	1330 through 1341
282	1 through 201	1 through 63	64 through 201	202	637 through 642	660 through 671
283	39 through 1034	39 through 134	135 through 1034	1035	1566 through 1571	
284	69 through 263	69 through 125	126 through 263	264	1173 through 1178	1587 through 1597
285	115 through 285	115 through 204	205 through 285	286	505 through 510	1196 through 1205
286	90 through 344	90 through 140	141 through 344	345	500 through 505	525 through 536
287	57 through 311	57 through 107	108 through 311	312	467 through 472	515 through 527
288	96 through 302	96 through 182	183 through 302	303	407 (1100g)1 472	482 through 493
289	161 through 526	161 through 328	329 through 526	527	1.	501 through 514
290	210 through 332	210 through 299	300 through 332	333		799 through 811
291	212 through 361	212 through 319	320 through 361	362	594 through 599	613 through 625
292	75 through 482	75 through 128	129 through 482		650 through 655	673 through 684
293	50 through 631	50 through 244		483	595 through 600	618 through 627
294	154 through 576		245 through 631	632	777 through 782	801 through 812
295	154 through 897	154 through 360	361 through 576	577	737 through 742	763 through 775
296	146 through 292	154 through 360	361 through 897	898	1017 through 1022	1044 through 1054
297	126 through 383	146 through 253	254 through 292	293	395 through 400	433 through 444
298		126 through 167	168 through 383	384	726 through 731	743 through 754
	66 through 497	66 through 239	240 through 497	498	594 through 599	618 through 629
299	49 through 411	49 through 96	97 through 411	412	732 through 737	750 through 763
300	49 through 534	49 through 96	97 through 534	535	593 through 598	612 through 623
301	86 through 415	86 through 145	146 through 415	416	540 through 545	560 through 571
302	56 through 268	56 through 100	101 through 268	269	584 through 589	601 through 612
303	32 through 328		104 through 328	329	508 through 513	528 through 539
304	21 through 527		96 through 527	528	921 through 926	953 through 963
305	147 through 647	147 through 374	375 through 647	648		668 through 681

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308	CON	NT. TABLE IV					
300	306	262 through 471	262 through 306	307 through 471	472	663 through 668	682 through 693
300	307	74 through 1216	74 through 172	173 through 1216	1217	1627 through 1632	1640 through 1652
310	308	48 through 164	48 through 89	90 through 164	165	482 through 487	505 through 517
311   90 through 815   90 through 179   180 through 815   816   883 through 888   905 through 916	309	185 through 334	185 through 295	296 through 334	335	355 through 360	392 through 405
312         52 through 513         52 through 533         232 through 533         151         55 through 558         572 through 583           313         172 through 438         172 through 354         355 through 368         439         682 through 877         685 through 697           314         148 through 366         148 through 276         277 through 360         367         770 through 775         792 through 803           315         175 through 336         175 through 276         277 through 553         337         .         812 through 813           316         181 through 336         191 through 304         305 through 553         554         766 through 771         804 through 813           317         106 through 603         106 through 261         217 through 558         587         1583 through 1588         1614 through 1623           318         47 through 566         47 through 561         217 through 581         315         1583 through 489         513 through 562         47 through 561         1614 through 1623           319         99 through 371         99 through 260         291 through 371         372         491 through 489         513 through 562         291 through 562         47 through 564         161 through 466         499 through 469         513 through 564         161 through 466 <td>310</td> <td>195 through 347</td> <td>195 through 272</td> <td>273 through 347</td> <td>348</td> <td>1037 through 1042</td> <td>1071 through 1082</td>	310	195 through 347	195 through 272	273 through 347	348	1037 through 1042	1071 through 1082
313   172 through 438   172 through 354   355 through 439   439   682 through 887   685 through 697	311	90 through 815	90 through 179	180 through 815	816	883 through 888	905 through 916
314   148 through 366	312	52 through 513	52 through 231	232 through 513	514	553 through 558	572 through 583
315         175 through 336         175 through 276         277 through 336         337         .         812 through 823           316         191 through 553         191 through 304         305 through 553         554         766 through 771         804 through 817           317         106 through 603         106 through 216         217 through 603         604         .         1102 through 1112           318         47 through 586         47 through 290         291 through 371         372         491 through 496         513 through 623           320         44 through 814         44 through 121         113 through 814         815         .         978 through 999           321         3 through 811         3 through 812         183 through 814         489 through 504         516 through 629           322         107 through 427         107 through 182         183 through 407         408         1008 through 504         516 through 504           322         107 through 427         107 through 251         252 through 332         333         .         869 through 80           325         217 through 543         217 through 251         252 through 344         447         930 through 81013         1032 through 1217           326         18 through 486         18 through 486<	313	172 through 438	172 through 354	355 through 438	439	682 through 687	685 through 697
316	314	148 through 366	148 through 225	226 through 366	367	770 through 775	792 through 803
317   106 through 603   106 through 216   217 through 603   604	315	175 through 336	175 through 276	277 through 336	337	·	812 through 823
318         47 through 586         47 through 124         125 through 586         587         1583 through 1588         1614 through 1623           319         99 through 371         99 through 290         291 through 371         372         491 through 496         513 through 524           320         44 through 814         44 through 112         113 through 814         815         -         978 through 999           321         3 through 427         107 through 180         191 through 427         428         499 through 504         516 through 529           323         45 through 427         107 through 83         84 through 407         408         1008 through 1013         1032 through 1042           324         201 through 332         201 through 251         252 through 332         333         -         869 through 880           325         217 through 543         217 through 255         256 through 543         544         -         1206 through 1217           326         18 through 446         18 through 440         141 through 446         447         930 through 935         948 through 939           327         29 through 724         29 through 426         467 through 526         587         1304 through 341         310 through 341         311 through 341         311 through 341	316	191 through 553	191 through 304	305 through 553	554	766 through 771	804 through 817
319         99 through 371         99 through 371         372         491 through 496         513 through 124           320         44 through 814         44 through 112         113 through 814         815         -         978 through 392           321         3 through 581         3 through 182         183 through 581         582         -         1006 through 1016           322         107 through 427         107 through 190         191 through 427         428         499 through 504         516 through 529           323         45 through 407         45 through 407         408         1008 through 1013         1032 through 1042           324         201 through 332         201 through 251         252 through 332         333         -         869 through 880           325         217 through 543         217 through 255         256 through 543         544         -         1206 through 920           327         29 through 724         29 through 148         119 through 724         725         886 through 891         910 through 920           328         404 through 566         467 through 565         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 432         331 through 432         331 through 565	317	106 through 603	106 through 216	217 through 603	604		1102 through 1112
320         44 through 814         44 through 112         113 through 814         815         -         978 through 989           321         3 through 581         3 through 182         183 through 581         582         -         1008 through 504         516 through 1016           322         107 through 427         107 through 83         84 through 427         428         499 through 504         516 through 529           323         45 through 407         45 through 332         201 through 251         252 through 332         333         -         869 through 880           325         217 through 543         217 through 255         256 through 543         544         -         1206 through 1217           326         18 through 446         18 through 140         141 through 446         447         930 through 935         948 through 959           327         29 through 724         29 through 118         119 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 549           330         59 through 752         351 through 752         753         -         1150 through 1161           331         672 throug	318	47 through 586	47 through 124	125 through 586	587	1583 through 1588	1614 through 1623
321         3 through 581         3 through 182         183 through 581         582         -         1008 through 1016           322         107 through 427         107 through 190         191 through 427         428         499 through 501         516 through 529           323         45 through 407         45 through 83         84 through 407         408         1008 through 1013         1032 through 1042           324         201 through 332         201 through 251         252 through 332         333         -         869 through 801           325         217 through 543         217 through 255         256 through 543         544         -         1206 through 1217           326         18 through 446         18 through 140         141 through 446         447         930 through 935         948 through 599           327         29 through 724         29 through 118         119 through 586         587         1304 through 1309         1334 through 124           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 722         221 through 722         723 through 703         704         886 through 891         903 through 914           3	319	99 through 371	99 through 290	291 through 371	372	491 through 496	513 through 524
322         107 through 427         107 through 190         191 through 427         428         499 through 504         516 through 529           323         45 through 407         45 through 251         252 through 332         333          869 through 880           324         201 through 543         217 through 251         252 through 543         544          1206 through 1217           326         18 through 448         18 through 140         141 through 446         447         930 through 935         948 through 959           327         29 through 724         29 through 118         119 through 446         447         930 through 891         910 through 959           328         404 through 586         404 through 466         467 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 220         221 through 703         704         886 through 891         903 through 904 through 905 sthrough 904 through 904 through 904 through 904 through 904	320	44 through 814	44 through 112	113 through 814	815		978 through 989
323         45 through 407         45 through 83         84 through 407         408         1008 through 1013         1032 through 1042           324         201 through 332         201 through 251         252 through 332         333         -         869 through 880           325         217 through 543         217 through 255         256 through 543         544         -         1206 through 1217           326         18 through 446         18 through 440         141 through 446         447         930 through 935         948 through 959           327         29 through 724         29 through 18         119 through 724         725         886 through 891         910 through 920           328         404 through 586         404 through 486         467 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 752         872 through 752         723 through 752         753         -         1150 through 1611           331         672 through 752         672 through 752         723 through 752         753         -         1150 through 363           332         57 through 311	321	3 through 581	3 through 182	183 through 581	582		1006 through 1016
324         201 through 332         201 through 251         252 through 332         333         -         869 through 880           325         217 through 543         217 through 255         256 through 543         544         -         1206 through 1217           326         18 through 446         18 through 446         147         930 through 935         948 through 959           327         29 through 724         29 through 118         119 through 724         725         886 through 891         910 through 990           328         404 through 586         404 through 466         467 through 586         587         1304 through 1309         1334 through 1344           329         331 through 322         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 220         221 through 703         704         886 through 891         903 through 914           331         672 through 752         872 through 722         723 through 311         312         332 through 337         351 through 363           333         90 through 291         19 through 291         128 through 291         292         367 through 372         389 through 645           334         91 through 384 <td< td=""><td>322</td><td>107 through 427</td><td>107 through 190</td><td>191 through 427</td><td>428</td><td>499 through 504</td><td>516 through 529</td></td<>	322	107 through 427	107 through 190	191 through 427	428	499 through 504	516 through 529
325         217 through 543         217 through 255         256 through 543         544         -         1206 through 1217           326         18 through 446         18 through 446         141 through 446         447         930 through 935         948 through 999           327         29 through 724         29 through 118         119 through 724         725         886 through 891         910 through 990           328         404 through 586         404 through 466         467 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 220         221 through 703         704         886 through 891         903 through 914           331         672 through 752         872 through 722         723 through 311         312         332 through 337         351 through 363           333         30 through 232         80 through 127         128 through 232         233         617 through 337         351 through 465           334         91 through 384         196 through 249         241 through 384         385         461 through 466         485 through 496           336 <td>323</td> <td>45 through 407</td> <td>45 through 83</td> <td>84 through 407</td> <td>408</td> <td>1008 through 1013</td> <td>1032 through 1042</td>	323	45 through 407	45 through 83	84 through 407	408	1008 through 1013	1032 through 1042
326         18 through 446         18 through 140         141 through 446         447         930 through 935         948 through 959           327         29 through 724         29 through 118         119 through 724         725         886 through 891         910 through 920           328         404 through 586         404 through 466         467 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 220         221 through 703         704         886 through 891         903 through 914           331         672 through 752         672 through 722         723 through 752         753         -         1150 through 914           332         57 through 311         57 through 128         129 through 311         312         332 through 337         351 through 363           333         80 through 232         80 through 219         128 through 232         233         617 through 372         389 through 645           334         91 through 291         91 through 219         220 through 221         292         367 through 372         389 through 496           336	324	201 through 332	201 through 251	252 through 332	333		869 through 880
327         29 through 724         29 through 118         119 through 724         725         886 through 891         910 through 920           328         404 through 586         404 through 466         467 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 722         221 through 703         704         886 through 891         903 through 914           331         672 through 752         672 through 722         723 through 752         753         -         1150 through 1161           332         57 through 311         57 through 128         129 through 311         312         332 through 337         351 through 363           333         80 through 232         80 through 231         128 through 232         233         617 through 622         634 through 645           334         91 through 291         91 through 291         292         367 through 372         389 through 400           335         196 through 384         196 through 240         241 through 384         385         461 through 466         485 through 496           337         133 through 846 <td>325</td> <td>217 through 543</td> <td>217 through 255</td> <td>256 through 543</td> <td>544</td> <td>-</td> <td>1206 through 1217</td>	325	217 through 543	217 through 255	256 through 543	544	-	1206 through 1217
328         404 through 586         404 through 486         467 through 586         587         1304 through 1309         1334 through 1344           329         331 through 432         331 through 387         388 through 432         433         548 through 553         573 through 585           330         59 through 703         59 through 722         221 through 703         704         886 through 891         903 through 914           331         672 through 752         672 through 722         723 through 752         753         -         1150 through 1161           332         57 through 311         57 through 128         129 through 311         312         332 through 337         351 through 363           333         80 through 232         80 through 127         128 through 232         233         617 through 622         634 through 645           334         91 through 291         91 through 291         292         367 through 372         389 through 400           335         196 through 384         196 through 240         241 through 384         385         461 through 466         485 through 496           336         54 through 590         54 through 345         346 through 866         847         -         890 through 965           337         133 through 846	326	18 through 446	18 through 140	141 through 446	447	930 through 935	948 through 959
329 331 through 432 331 through 387 388 through 432 433 548 through 553 573 through 585 330 59 through 703 59 through 220 221 through 703 704 886 through 891 903 through 914 331 672 through 752 672 through 722 723 through 752 753	327	29 through 724	29 through 118	119 through 724	725	886 through 891	910 through 920
330         59 through 703         59 through 220         221 through 703         704         886 through 891         903 through 914           331         672 through 752         672 through 752         723 through 752         753         .         1150 through 1161           332         57 through 311         57 through 128         129 through 311         312         332 through 337         351 through 363           333         80 through 232         80 through 127         128 through 232         233         617 through 622         634 through 645           334         91 through 291         91 through 219         220 through 384         385         461 through 466         485 through 496           336         54 through 590         54 through 227         228 through 590         591         .         955 through 965           337         133 through 846         133 through 345         346 through 846         847         .         890 through 901           338         138 through 671         138 through 486         133 through 486         847         .         890 through 901           339         124 through 411         124 through 486         187 through 486         847         .         890 through 983           340         372 through 484         372 through 4	328	404 through 586	404 through 466	467 through 586	587	1304 through 1309	1334 through 1344
331       672 through 752       672 through 722       723 through 752       753       .       1150 through 1161         332       57 through 311       57 through 128       129 through 311       312       332 through 337       351 through 363         333       80 through 232       80 through 127       128 through 232       233       617 through 622       634 through 645         334       91 through 291       91 through 219       220 through 291       292       367 through 372       389 through 400         335       196 through 384       196 through 240       241 through 384       385       461 through 466       485 through 496         336       54 through 590       54 through 227       228 through 590       591       -       955 through 965         337       133 through 846       133 through 345       346 through 846       847       -       890 through 901         338       138 through 671       138 through 248       249 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 494       444 through 192       193 through 450       451	329	331 through 432	331 through 387	388 through 432	433	548 through 553	573 through 585
332       57 through 311       57 through 128       129 through 311       312       332 through 337       351 through 363         333       80 through 232       80 through 127       128 through 232       233       617 through 622       634 through 645         334       91 through 291       91 through 219       220 through 291       292       367 through 372       389 through 400         335       196 through 384       196 through 240       241 through 384       385       461 through 466       485 through 496         336       54 through 590       54 through 345       346 through 846       847       -       955 through 965         337       133 through 846       133 through 345       346 through 846       847       -       890 through 901         338       138 through 671       138 through 248       249 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 465       451       1053 thr	330	59 through 703	59 through 220	221 through 703	704	886 through 891	903 through 914
333       80 through 232       80 through 127       128 through 232       233       617 through 622       634 through 645         334       91 through 291       91 through 219       220 through 291       292       367 through 372       389 through 400         335       196 through 384       196 through 240       241 through 384       385       461 through 466       485 through 496         336       54 through 590       54 through 227       228 through 590       591       -       955 through 965         337       133 through 846       133 through 345       346 through 846       847       -       890 through 901         338       138 through 671       138 through 248       249 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 776       76 through 718       719       117	331	672 through 752	672 through 722	723 through 752	753		1150 through 1161
334       91 through 291       91 through 219       220 through 291       292       367 through 372       389 through 400         335       196 through 384       196 through 240       241 through 384       385       461 through 466       485 through 496         336       54 through 590       54 through 227       228 through 590       591       -       955 through 965         337       133 through 846       133 through 345       346 through 846       847       -       890 through 901         338       138 through 671       138 through 248       249 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 71       171 through 866       867       1159 through 1164       1178 through 1170       178 through 71       170 through 718       1170 through 716       1203 through 1213         34	332	57 through 311	57 through 128	129 through 311	312	332 through 337	351 through 363
335       196 through 384       196 through 240       241 through 384       385       461 through 466       485 through 496         336       54 through 590       54 through 227       228 through 590       591       -       955 through 965         337       133 through 846       133 through 345       346 through 846       847       -       890 through 901         338       138 through 671       138 through 248       249 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 866       867       1159 through 1164       1178 through 1190         343       13 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 709       710       943 through 948       963 through 973 <td>333</td> <td>80 through 232</td> <td>80 through 127</td> <td>128 through 232</td> <td>233</td> <td>617 through 622</td> <td>634 through 645</td>	333	80 through 232	80 through 127	128 through 232	233	617 through 622	634 through 645
336       54 through 590       54 through 227       228 through 590       591       -       955 through 965         337       133 through 846       133 through 345       346 through 846       847       -       890 through 901         338       138 through 671       138 through 248       249 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 170       171 through 866       867       1159 through 1164       1178 through 1190         343       13 through 465       13 through 75       76 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 973         345       86 through 709       86 through 320       321       771 through 776 <td< td=""><td>334</td><td>91 through 291</td><td>91 through 219</td><td>220 through 291</td><td>292</td><td>367 through 372</td><td>389 through 400</td></td<>	334	91 through 291	91 through 219	220 through 291	292	367 through 372	389 through 400
337       133 through 846       133 through 345       346 through 846       847       -       890 through 901         338       138 through 671       138 through 248       249 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 866       867       1159 through 1164       1178 through 1190         343       13 through 465       13 through 75       76 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321       771 through 776	335	196 through 384	196 through 240	241 through 384	385	461 through 466	485 through 496
338       138 through 671       138 through 248       249 through 671       672       1319 through 1324       1338 through 1347         339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 170       171 through 866       867       1159 through 1164       1178 through 1190         343       13 through 465       13 through 75       76 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321       771 through 776       799 through 810	336	54 through 590	54 through 227	228 through 590	591		955 through 965
339       124 through 411       124 through 186       187 through 411       412       948 through 953       971 through 983         340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 866       867       1159 through 1164       1178 through 1190         343       13 through 465       13 through 75       76 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321       771 through 776       799 through 810	337	133 through 846	133 through 345	346 through 846	847	-	890 through 901
340       372 through 494       372 through 443       444 through 494       495       708 through 713       732 through 745         341       112 through 450       112 through 192       193 through 450       451       1053 through 1058       1095 through 1106         342       117 through 866       117 through 170       171 through 866       867       1159 through 1164       1178 through 1190         343       13 through 465       13 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321       771 through 776       799 through 810	338	138 through 671	138 through 248	249 through 671	672	1319 through 1324	1338 through 1347
341 112 through 450 112 through 192 193 through 450 451 1053 through 1058 1095 through 1106 342 117 through 866 117 through 170 171 through 866 867 1159 through 1164 1178 through 1190 343 13 through 465 13 through 75 76 through 465 466 1035 through 1040 1060 through 1070 344 2 through 718 2 through 76 77 through 718 719 1170 through 1175 1203 through 1213 345 86 through 709 86 through 361 362 through 709 710 943 through 948 963 through 973 346 63 through 320 63 through 179 180 through 320 321 771 through 776 799 through 810	339	124 through 411	124 through 186	187 through 411	412	948 through 953	971 through 983
342       117 through 866       117 through 170       171 through 866       867       1159 through 1164       1178 through 1190         343       13 through 465       13 through 75       76 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321       771 through 776       799 through 810	340	372 through 494	372 through 443	444 through 494	495	708 through 713	732 through 745
343       13 through 465       13 through 75       76 through 465       466       1035 through 1040       1060 through 1070         344       2 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321       771 through 776       799 through 810	341	112 through 450	112 through 192	193 through 450	451	1053 through 1058	1095 through 1106
344       2 through 718       2 through 76       77 through 718       719       1170 through 1175       1203 through 1213         345       86 through 709       86 through 361       362 through 709       710       943 through 948       963 through 973         346       63 through 320       63 through 179       180 through 320       321       771 through 776       799 through 810	342	117 through 866	117 through 170	171 through 866	867	1159 through 1164	1178 through 1190
345 86 through 709 86 through 361 362 through 709 710 943 through 948 963 through 973 346 63 through 320 63 through 179 180 through 320 321 771 through 776 799 through 810	343	13 through 465	13 through 75	76 through 465	466	1035 through 1040	1060 through 1070
346 63 through 320 63 through 179 180 through 320 321 771 through 776 799 through 810	344	2 through 718	2 through 76	77 through 718	719	1170 through 1175	1203 through 1213
AAT COO	345	86 through 709	86 through 361	362 through 709	710	943 through 948	963 through 973
347   299 through 418   299 through 379   380 through 418   419   739 through 744   762 through 771	346	63 through 320	63 through 179	180 through 320	321	771 through 776	799 through 810
1 702 till tolgh 771	347	299 through 418	299 through 379	380 through 418	419	739 through 744	762 through 771

CONT. TABLE IV

CUNT	I, I ADLE IV					
348	186 through 380	186 through 233	234 through 380	381	383 through 388	396 through 409
349	69 through 458	69 through 233	234 through 458	459	564 through 569	602 through 613
350	12 through 638	12 through 263	264 through 638	639	951 through 956	975 through 985
351	282 through 389	282 through 332	333 through 389	390	1413 through 1418	1437 through 1447
352	208 through 339	208 through 294	295 through 339	340		1631 through 1641
353	69 through 557	69 through 224	225 through 557	558	849 through 854	870 through 883
354	134 through 325	134 through 274	275 through 325	326		718 through 729
355	78 through 731	78 through 227	228 through 731	732		1002 through 1013
356	46 through 693	46 through 90	91 through 693	694	937 through 942	962 through 973
<b>3</b> 57	126 through 527	126 through 182	183 through 527	528	834 through 839	856 through 867
358	66 through 320	66 through 113	114 through 320	321	490 through 495	508 through 519
359	73 through 948	73 through 159	160 through 948	949	-	1016 through 1028
360	69 through 434	69 through 236	237 through 434	435	419 through 424	441 through 452
361	628 through 804	628 through 711	712 through 804	805		864 through 875
362	70 through 366	70 through 108	109 through 366	367	496 through 501	521 through 531
363	70 through 366	70 through 108	109 through 366	367		1233 through 1244
364	111 through 434	111 through 185	186 through 434	435	-	618 through 631
365	19 through 567	19 through 63	64 through 567	568	749 through 754	771 through 781
366	19 through 312	19 through 63	64 through 312	313	896 through 901	921 through 931
367	64 through 612	64 through 234	235 through 612	613	·	839 through 849
368	39 through 458	39 through 80	81 through 458	459	613 through 618	633 through 644
369	9 through 185	9 through 50	51 through 185	186	·	906 through 918
370	14 through 316	14 through 121	122 through 316	317	442 through 447	458 through 471
371	70 through 1092	70 through 234	235 through 1092	1093	1475 through 1480	1493 through 1504
372	274 through 597	274 through 399	400 through 597	598	731 through 736	754 through 765
373	230 through 469	230 through 307	308 through 469	470	1004 through 1009	1027 through 1040
374	72 1hrough 545	72 through 203	204 through 545	546	·	1151 through 1162
375	36 through 425	36 through 119	120 through 425	426	1215 through 1220	1240 through 1250
376	155 through 751	155 through 340	341 through 751	752	912 through 917	937 through 947
377	46 through 585	46 through 120	121 through 585	586	584 through 589	606 through 619

TABLE V

lď	Full Length Polypeptide Location	Signal Peptide Location	Mature Polypeptide Location
141	-31 through 124	-31 through -1	1 through 124
142	1 through 55		1 through 55
143	-20 through 47	-20 through -1	1 through 47
144	-21 through 177	-21 through -1	1 through 177
145	-25 through 110	-25 through -1	1 through 110
146	-70 through 185	-70 through -1	1 through 185
147	-49 through 10	-49 through -1	1 through 10
148	1 through 180		1 through 180
149	-23 through 139	-23 through -1	1 through 139
150	-23 through 97	-23 through -1	1 through 97
151	1 through 7	23 till dagil 1	
152	-42 through 157	-42 through -1	1 through 7
153	1 through 43	- Tribugh 1	1 through 157
154	-37 through 13	-37 through -1	1 through 43
155	1 through 153	-ov minnihi vi	1 through 13
156	1 through 67		1 through 153
157	1 through 87		1 through 67
158	-85 through 165	-85 through -1	1 through 87
159	1 through 24	-05 (mough - )	1 through 165
160	1 through 228		1 through 24
161	-20 through 66	20 sharan 1	1 through 228
162	1 through 44	-20 through -1	1 through 66
163	-58 through 256		1 through 44
164	-80 through 9	-58 through -1	1 through 256
165	-15 through 83	-80 through -1	1 through 9
166	-36 through 56	-15 through -1	1 through 83
167	-16 through 335	36 through -1	1 through 56
168	-47 through 91	-16 through -1	1 through 335
169	-73 through 28	-47 through -1	1 through 91
170		-73 through -1	1 through 28
171	-68 through 184	-68 through -1	1 through 184
172	-68 through 282	-68 through -1	1 through 282
173	-68 through 322	-68 through -1	1 through 322
174	-82 through 108	-82 through -1	1 through 108
175	-232 through 53	-232 through -1	1 through 53
176	1 through 153		1 through 153
176	1 through 49		1 through 49
178	-24 through 75	-24 through -1	1 through 75
179	-37 through 58	-37 through -1	1 through 58
180	-23 through 98	-23 through -1	1 through 98
181	1 through 59		1 through 59
	-14 through 72	-14 through -1	1 through 72
182	-58 through 107	-58 through -1	1 through 107
183	-35 through 45	-35 through -1	1 through 45
184	-21 through 52	-21 through -1	1 through 52
185	1 through 98	·	1 through 98
186	-21 through 91	-21 through -1	1 through 91
187	-44 through 26	-44 through -1	1 through 26
88	-13 through 79	-13 through -1	1 through 79
89	-42 through 165	-42 through -1	1 through 165
90	1 through 201		1 through 201

191	-37 through 342	-37 through -1	1 through 342
192	1 through 112	·	1 through 112
193	1 through 43	<u>.</u>	1 through 43
194	-16 through 35	-16 through -1	1 through 35
195	-18 through 226	-18 through -1	1 through 226
196	-34 through 319	-34 through -1	1 through 319
197	1 through 30	•	1 through 30
198	-48 through 64	-48 through -1	1 through 64
199	1 through 54		1 through 54
200	-21 through 130	-21 through -1	1 through 130
201	-25 through 203	-25 through -1	1 through 203
202	-47 through 17	-47 through -1	1 through 17
203	-31 through 115	-31 through -1	1 through 115
204	1 through 87	•	1 through 87
205	-27 through 13	-27 through -1	1 through 13
206	1 through 154		1 through 154
207	1 through 101		1 through 101
208	-22 through 434	-22 through -1	1 through 434
209	-17 through 81	-17 through -1	1 through 81
210	-29 through 54	-29 through -1	1 through 54
211	-23 through 206	-23 through -1	1 through 206
212	-21 through 131	-21 through -1	1 through 131
213	-54 through 125	-54 through -1	1 through 125
214	-92 through 177	-92 through -1	1 through 177
215	-22 through 113	-22 through -1	1 through 113
216	-38 through 29	-38 through -1	1 through 29
217	-54 through 71	-54 through -1	1 through 71
218	-21 through 355	-21 through -1	1 through 355
219	-30 through 181	-30 through -1	1 through 181
220	-60 through 94	-60 through -1	1 through 94
221	-42 through 81	-42 through -1	1 through 81
222	-19 through 327	-19 through -1	1 through 327
223	-20 through 190	-20 through -1	1 through 190
224	-20 through 164	-20 through -1	1 through 164
225	-22 through 205	-22 through -1	1 through 205
226	-41 through 33	-41 through -1	1 through 33
227	1 through 73		1 through 73
228	-16 through 66	-16 through -1	1 through 66
229	-56 through 63	-56 through -1	1 through 63
230	1 through 54		1 through 54
231	-14 through 196	-14 through -1	1 through 196
232	1 through 108		1 through 108
233	-18 through 25	-18 through -1	1 through 25
234	1 through 36		1 through 36
235	-13 through 294	-13 through -1	1 through 294
236	-32 through 74	-32 through -1	1 through 74
237	-19 through 23	-19 through -1	1 through 23
238	-20 through 97	-20 through -1	1 through 97
239	-37 through 141	-37 through -1	1 through 141
240	-27 through 99	-27 through -1	1 through 99
241	-115 through 59	-115 through -1	1 through 59
	-20 through 32	-20 through -1	1 through 32
378	-20 through 170	-23 through -1	1 through 170

ONT. TABLE V			
381	-21 through 177	-21 through -1	1 through 177
382	-55 through 105	-55 through -1	1 through 105
383	-18 through 90	-18 through -1	1 through 90
384	-22 through 42	-22 through -1	1 through 42
385	-15 through 12	-15 through -1	1 through 12
386	-21 through 165	-21 through -1	1 through 165
387	-26 through 153	-26 through -1	1 through 153
388	-55 through 95	-55 through -1	1 through 95
389	-31 through 205	-31 through -1	1 through 205
390	-100 through 49	-100 through -1	1 through 49
391	-49 through 20	-49 through -1	1 through 20
392	-30 through 211	-30 through -1	1 through 211
393	-30 through 17	-30 through -1	1 through 17
394	-28 through 37	-28 through -1	1 through 37
395	-24 through 49	-24 through -1	1 through 49
396	-18 through 42	·18 through ·1	1 through 42
397	-93 through 99	-93 through -1	1 through 99
398	-72 through 77	-72 through -1	1 through 77
399	-20 through 53	-20 through -1	1 through 53
400	-20 through 66	-20 through -1	1 through 66
401	-21 through 57	-21 through -1	1 through 57
402	-28 through 37	-28 through -1	1 through 37
403	-27 through 184	-27 through -1	1 through 184
404	-80 through 43	-80 through -1	1 through 43
405	-26 through 60	-26 through -1	1 through 60
406	-31 through 131	-31 through -1	1 through 131
407	-37 through 61	-37 through -1	1 through 61
408	-15 through 55	-15 through -1	1 through 55
409	-45 through 15	-45 through -1	1 through 15
410	-22 through 17	-22 through -1	1 through 17
411	-23 through 28	-23 through -1	1 through 28
412	-48 through 47	-48 through -1	1 through 47
413	-32 through 28	-32 through -1	1 through 28
414	-79 through 91	-79 through -1	1 through 91
415	-82 through 108	-82 through -1	1 through 108
416	-60 through 54	-60 through -1	1 through 54
417	-108 through 53	-108 through -1	1 through 53
418	-21 through 46	-21 through -1	1 through 46
419	-32 through 300	-32 through -1	1 through 300
420	-19 through 46	-19 through -1	1 through 46
422	-30 through 27	-30 through -1	1 through 27
423	-17 through 68	-17 through -1	1 through 68
424	-17 through 68	-17 through -1	1 through 68
425			
426	-29 through 40	-29 through -1	
720	-29 through 40 -56 through 66	-29 through -1 -56 through -1	1 through 40
427		-56 through -1	1 through 40 1 through 66
	-56 through 66	-56 through -1 -30 through -1	1 through 40 1 through 66 1 through 11
427	-56 through 66 -30 through 11 -36 through 14	-56 through -1 -30 through -1 -36 through -1	1 through 40 1 through 66 1 through 11 1 through 14
427 428	-56 through 66 -30 through 11 -36 through 14 -18 through 118	-56 through -1 -30 through -1 -36 through -1 -18 through -1	1 through 40 1 through 66 1 through 11 1 through 14 1 through 118
427 428 429 430	-56 through 66 -30 through 11 -36 through 14 -18 through 118 -65 through 129	-56 through -1 -30 through -1 -36 through -1 -18 through -1 -65 through -1	1 through 40 1 through 66 1 through 11 1 through 14 1 through 118 1 through 129
427 428 429 430 431	-56 through 66 -30 through 11 -36 through 14 -18 through 118 -65 through 129 -69 through 72	-56 through -1 -30 through -1 -36 through -1 -18 through -1 -65 through -1 -69 through -1	1 through 40 1 through 66 1 through 11 1 through 14 1 through 118 1 through 129 1 through 72
427 428 429 430 431 432	-56 through 66 -30 through 11 -36 through 14 -18 through 118 -65 through 129 -69 through 72 -69 through 179	-56 through -1 -30 through -1 -36 through -1 -18 through -1 -65 through -1 -69 through -1 -69 through -1	1 through 40 1 through 66 1 through 11 1 through 14 1 through 118 1 through 129 1 through 72 1 through 179
427 428 429 430 431	-56 through 66 -30 through 11 -36 through 14 -18 through 118 -65 through 129 -69 through 72	-56 through -1 -30 through -1 -36 through -1 -18 through -1 -65 through -1 -69 through -1	1 through 40 1 through 66 1 through 11 1 through 14 1 through 118 1 through 129 1 through 72

CONT. TABLE V

ONT. TABLE \	V		
436	-16 through 105	-16 through -1	1 through 105
437	-16 through 146	-16 through -1	1 through 146
438	-20 through 90	-20 through -1	1 through 90
439	-15 through 56	-15 through -1	1 through 56
440	-24 through 75	-24 through -1	1 through 75
441	-25 through 144	-25 through -1	1 through 144
442	-76 through 91	-76 through -1	1 through 91
443	-15 through 55	-15 through -1	1 through 55
444	-33 through 348	-33 through -1	1 through 348
445	-14 through 25	-14 through -1	1 through 25
446	-37 through 13	-37 through -1	1 through 13
447	-26 through 25	-26 through -1	1 through 25
448	-30 through 212	-30 through -1	
449	-60 through 94	-60 through -1	1 through 212
450	-61 through 28	-61 through -1	1 through 94
451	-26 through 47	-26 through -1	1 through 28
452	-34 through 20	-34 through -1	1 through 47
453	-38 through 83	-38 through -1	1 through 20
454	-37 through 129	-37 through -1	1 through 83
455	-26 through 154	-26 through -1	1 through 129
456	-64 through 27	-64 through -1	1 through 154
457	-23 through 234	-23 through -1	1 through 27
458	-60 through 133	-60 through -1	1 through 234
459	-28 through 79	-28 through -1	1 through 133
460	-13 through 108	-13 through -1	1 through 79
461	-17 through 27	-17 through -1	1 through 108
462	-13 through 96	-13 through -1	1 through 27
463	-41 through 102	-41 through -1	1 through 96
464	-30 through 202	-30 through -1	1 through 102
465	-21 through 40	-21 through -1	1 through 202
466	-19 through 15	-19 through -1	1 through 40
467	-54 through 161		1 through 15
468	-17 through 10	-54 through -1 -17 through -1	1 through 161
469	-24 through 61		1 through 10
470	-16 through 35	-24 through -1	1 through 61
471	-43 through 24	-16 through -1	1 through 35
472	-15 through 48	-43 through -1	1 through 24
473	-58 through 121	-15 through -1	1 through 48
474	-71 through 167	-58 through -1	1 through 121
475	-37 through 141	-71 through -1	1 through 167
476	-21 through 75	-37 through -1	1 through 141
477	-24 through 17	-21 through -1	1 through 75
478	-24 through 17	-24 through -1	1 through 17
479	-18 through 232	-27 through -1	1 through 86
480		-18 through -1	1 through 232
481	-21 through 130 -25 through 214	-21 through -1	1 through 130
482		-25 through -1	1 through 214
483	-92 through 116	-92 through -1	1 through 116
484	-39 through 47	-39 through -1	1 through 47
485	-27 through 13	-27 through -1	1 through 13
486	-16 through 49	-16 through -1	1 through 49
	-55 through 75	-55 through -1	1 through 75
487	-84 through 125	-84 through -1	1 through 125
488	-17 through 19	-17 through -1	1 through 19
489	-29 through 15	-29 through -1	. 1 through 15

490	-52 through 111	-52 through -1	1 through 111
491	-47 through 17		1 through 111
492	·	-47 through -1	1 through 17
	-50 through 168	-50 through -1	1 through 168
493	-15 through 201	-15 through -1	1 through 201
494	-19 through 115	-19 through -1	1 through 115
495	-16 through 69	-16 through -1	1 through 69
496	-29 through 263	-29 through -1	1 through 263
497	-56 through 66	-56 through -1	1 through 66
498	-28 through 31	-28 through -1	1 through 31
499	-13 through 86	-13 through -1	1 through 86
500	-13 through 86	-13 through -1	1 through 86
501	-25 through 83	-25 through -1	1 through 83
502	-15 through 168	-15 through -1	1 through 168
503	-15 through 83	-15 through -1	1 through 83
504	-57 through 126	-57 through -1	1 through 126
505	-14 through 126	-14 through -1	1 through 126
506	-14 through 45	-14 through -1	1 through 45
507	-36 through 65	-36 through -1	1 through 65
508	-55 through 286	-55 through -1	1 through 286
509	-42 through 66	-42 through -1	1 through 66
510	-26 through 54	-26 through -1	1 through 54
511	-44 through 114	-44 through -1	1 through 114
512	-28 through 102	-28 through -1	1 through 102
513	-62 through 137	-62 through -1	1 through 137
514	-25 through 155	-25 through -1	1 through 155

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ld	Collection refs	Deposit Name
40	ATCC # 98921	SignalTag 121-144
41	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
42	ATCC # 98921	SignalTag 121-144
43	ATCC # 98920	SignalTag 67-90
44	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
45	ATCC # 98920	SignalTag 67:90
46	ATCC # 98923	SignalTag 44-66
47	ATCC # 98920	SignalTag 67:90
48	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
49	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
50	ATCC # 98921	SignalTag 121-144
51	ATCC # 98921	SignalTag 121·144
52	ATCC # 98920	SignalTag 67-90
53	ATCC # 98923	SignalTag 44-66
54	ATCC # 98920	SignalTag 67-90
55	ATCC # 98920	SignalTag 67-90
56	ATCC # 98920	SignalTag 67-90
57	ATCC # 98921	SignalTag 121·144
58	ATCC # 98920	SignalTag 67-90
59	ATCC # 98920	SignalTag 67-90
60	ATCC # 98920	SignalTag 67-90
61	ATCC # 98923	SignalTag 44-66
62	ATCC # 98923	SignalTag 44-66
63	ATCC # 98923	SignalTag 44-66
64	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
65	ATCC # 98923	SignalTag 44-66
66	ATCC # 98921	SignalTag 121·144
67	ATCC # 98920	SignalTag 67-90
68	ATCC # 98920	SignalTag 67-90
69	ATCC # 98921	SignalTag 121-144
70	ATCC # 98921	SignalTag 121-144
71	ATCC # 98921	SignalTag 121-144
72	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
73	ATCC # 98923	SignalTag 44-66

		121.
74	ATCC # 98923	SignalTag 44-66
75	ATCC # 98920	SignalTag 67-90
76	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
77	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
78	ATCC # 98921	SignalTag 121-144
79	ATCC # 98923	SignalTag 44-66
80	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
81	ATCC # 98921	SignalTag 121-144
82	ATCC # 98920	SignalT ag 67-90
83	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
84	ATCC # 98923	SignalTag 44-66
85	ATCC # 98923	SignalTag 44-66
86	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
87	ATCC # 98923	SignalTag 44-66
88	ATCC # 98923	SignalTag 44-66
89	ATCC # 98923	SignalTag 44-66
90	ATCC # 98923	SignalTag 44-66
91	ATCC # 98923	SignalTag 44-66
92	ATCC # 98920	SignalTag 67-90
93	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
94	ATCC # 98923	SignalTag 44-66
95	ATCC # 98923	SignalTag 44-66
96	ATCC # 98920	SignalTag 67-90
97	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
98	ATCC # 98921	SignalTag 121-144
99	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
100	ATCC # 98921	SignalTag 121-144
101	ATCC # 98920	SignalTag 67-90
102	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
103	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
104	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
105	ATCC # 98921	SignalTag 121-144
106	ATCC # 98920	SignalTag 67-90
107	ATCC # 98920	SignalTag 67-90
108	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
109	ATCC # 98923	SignalTag 44-66
110	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120

111	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120.
112	ATCC # 98920	SignalTag 67-90
113	ATCC # 98920	SignalTag 67-90
114	ATCC # 98923	SignalTag 44-66
115	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
116	ATCC # 98920	SignalTag 67-90
117	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
118	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
119	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
120	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
121	ATCC # 98923	SignalTag 44-66
122	ATCC # 98920	SignalTag 67-90
123	ATCC # 98920	SignalTag 67-90
124	ATCC # 98922	SignalTag 91-94, 96, 97, 99-107, 109-112 et 114-120
125	ECACC # 98121506	SignalTag 11121998
126	ECACC # 98121506	SignalTag 11121998
127	ECACC # 98121506	SignalTag 11121998
128	ECACC # 98121506	SignalTag 11121998
129	ECACC # 98121506	SignalTag 11121998
130	ECACC # 98121506	SignalTag 11121998
131	ECACC # 98121506	SignalTag 11121998
132	ECACC # 98121506	SignalTag 11121998
133	ECACC # 98121506	SignalTag 11121998
134	ECACC # 98121506	SignalTag 11121998
135	ECACC # 98121506	SignalTag 11121998
136	ECACC # 98121506	SignalTag 11121998
137	ECACC # 98121506	SignalTag 11121998
138	ECACC # 98121506	SignalTag 11121998
39	ECACC # 98121506	SignalTag 11121998
40	ECACC # 98121506	SignalTag 11121998

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**TABLE VII** 

	IAB	LARLE VII	
Internal designation number	SEQ ID NO	Type of sequence	
20-5-2-C3-CL0_4	40	DNA	
20-8-4-A11-CL2_6	41	DNA	
21-1-4-F2-CL11_1	42	DNA	
22-11-2-H9-CL1_1	43	DNA	
25-7-3-D4-CL0_2	44	DNA	
26-27-3-D7-CLO_1	45	DNA	
26-35-4-H9-CL1_1	46	DNA	
26-45-2-C4-CL2_6	47	DNA	
27-1-2-B3-CLO_1	48	DNA	
27-1-2- <b>B3-CL</b> 0_2	49	DNA	
27-19-3-G7-CL11_2	50	DNA	
33-10-4-E2-CL13_4	51	DNA	
33-10-4-H2-CL2_2	52	DNA	
33-110-4-A5-CL1_1	53	DNA	
33-13-1-C1-CL1_1	54	DNA	
33-30-2-A6-CL0_1	55	DNA	
33-35-4-F4-CL1_2	56	DNA	
33-35-4-G1-CL1_2	57	DNA	
33-36-3-E2-CL1_1	58	DNA	
33-36-3-E2-CL1_2	<b>5</b> 9	DNA	
33-36-3-F2-CL2_2	60	DNA	
33-4-2-G5-CL2_1	61	DNA	
33-49-1-H4-CL1_1	62	DNA	
33-66-2-B10-CL4_1	63	DNA	
33-97-4-G8-CL2_2	64	DNA	
33-98-4-C1-CL1_3	65	DNA	
47-14-1-C3-CLO_5	66	DNA	
47-15-1-E11-CLO_1	67	DNA	
47-15-1-H8-CL0_2	68	DNA	
48-1-1-H7-CL0_1	69	DNA	
48-1-1-H7-CL0_4	70	DNA	
48-1-1-H7-CLO_5	71	DNA	
48-3-1-H9-CL0_6	72	DNA	
48-54-1-G9-CL2_1	73	DNA	

48-54-1-G9-CL3_1	74	DNA
48-7-4-H2-CL2_2	75	DNA
51-11-3-D5-CL1_3	76	DNA
51-11-3-G9-CLO_1	77	DNA
51-15-4-A12-CL11_3	78	DNA
51-17-4-A4-CL3_1	79	DNA
51-2-3-F10-CL1_5	80	DNA
51-2-4-F5-CL11_2	81	DNA
51-27-4-F2-CLO_2	82	DNA
51-34-3-F8-CLO_2	83	DNA
57-1-4-E2-CL1_2	84	DNA
57-19-2-G8-CL2_1	85	DNA
57-27-3-G10-CL2_2	86	DNA
58-33-3-B4-CL1_2	87	DNA
58-34-3-C9-CL1_2	88	DNA
58-4-4-G2-CL2_1	89	DNA
58-48-1-G3-CL2_4	90	DNA
58-6-1-H4-CL1_1	91	DNA
60-12-1-E11-CL1_2	92	DNA
65-4-4-H3-CL1_1	93	DNA
74-5-1-E4-CL1_2	94	DNA
76-13-3-A9-CL1_2	95	DNA
76-16-1-D6-CL1_1	96	DNA
76-28-3-A12-CL1_5	97	DNA
76-42-2-F3-CLO_1	98	DNA
77-16-4-G3-CL1_3	99	DNA
77-39-4-H4-CL11_4	100	DNA
78-24-3-H4-CL2_1	101	DNA
78-27-3-D1-CL1_6	102	DNA
78-28-3-D2-CLO_2	103	DNA
78-7-1-G5-CL2_6	104	DNA
84-3-1-G10-CL11_6	105	DNA
58-48-4-E2-CL0_1	106	DNA
23-12-2-G6-CL1_2	107	DNA
25-8-4-B12-CL0_5	108	DNA
26-44-3-C5-CL2_1	109	DNA
27-1-2-B3-CLO_3	110	DNA

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30-12-3-G5-CL0_1	111	DNA
33-106-2-F10-CL1_3	112	DNA
33-28-4-D1-CLO_1	113	DNA
33-31-3-C8-CL2_1	114	DNA
48-24-1-D2-CL3_2	115	DNA
48-46-4-A11-CL1_4	116	DNA
51-1-4-C1-CL0_2	117	DNA
51-39-3-H2-CL1_2	118	DNA
51-42-3-F9-CL1_1	119	DNA
51-5-3-G2-CL0_4	120	DNA
57-18-4-H5-CL2_1	121	DNA
76-23-3- <b>G</b> 8-CL1_1	122	DNA
76-23-3- <b>G8-CL</b> 1_3	123	DNA
78-8-3-E6-CLO_1	124	DNA
19-10-1-C2-CL1_3	125	DNA
33-11-1-B11-CL1_2	126	DNA
33-113-2-B8-CL1_2	127	DNA
33-19-1-C11-CL1_1	128	DNA
33-61-2-F6-CLO_2	129	DNA
47-4-4-C6-CL2_2	130	DNA
48-54-1-G9-CL1_1	131	DNA
51-43-3-G3-CLO_1	132	DNA
55-1-3-D11-CLO_1	133	DNA
58-14-2-D3-CL1_2	134	DNA
58-35-2-B6-CL2_3	135	DNA
76-18-1-F6-CL1_1	136	DNA
76-23-3-G8-CL2_2	137	DNA
76-30-3-B7-CL1_1	138	DNA
78-21-3-G7-CL2_1	139	DNA
58-45-4-B11-CL13_2	140	DNA
20·5·2·C3·CL0_4	141	PRT
20-8-4-A11-CL2_6	142	PRT
21-1-4-F2-CL11_1	143	PRT
22-11-2-H9-CL1_1	144	PRT
25-7-3-D4-CLO_2	145	PRT
26-27-3-D7-CLO_1	146	PRT
26-35-4-H9-CL1_1	147	PRT

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26-45-2-C4-CL2_6	148	PRT
27-1-2-B3-CLO_1	149	PRT
27-1-2-B3-CLO_2	150	PRT
27-19-3-67-CL11_2	151	PRT
33-10-4-E2-CL13_4	152	PRT
33-10-4-H2-CL2_2	153	PRT
33-110-4-A5-CL1_1	154	PRT
33-13-1-C1-CL1_1	155	PRT
33-30-2-A6-CLO_1	156	PRT
33-35-4-F4-CL1_2	157	PRT
33-35-4-G1-CL1_2	158	PRT
33-36-3-E2-CL1_1	159	PRT
33-36-3-E2-CL1_2	160	PRT
33-36-3-F2-GL2_2	161	PRT
33-4-2-G5-CL2_1	162	PRT
33-49-1-H4-CL1_1	163	PRT
33-66-2-B10-CL4_1	164	PRT
33-97-4-G8-CL2_2	165	PRT
33-98-4-C1-CL1_3	166	PRT
47-14-1-C3-CL0_5	167	PRT
47-15-1-E11-CL0_1	168	PRT
47-15-1-H8-CLO_2	169	PRT
48-1-1-H7-CLO_1	170	PRT
48-1-1-H7-CLO_4	171	PRT
48-1-1-H7-CL0_5	172	PRT
48-3-1-H9-CL0_6	173	PRT
48-54-1-G9-CL2_1	174	PRT
48-54-1-G9-CL3_1	175	PRT
48-7-4-H2-CL2_2	176	PRT
51-11-3-D5-CL1_3	177	PRT
51-11-3-G9-CLO_1	178	PRT
51-15-4-A12-CL11_3	179	PRT
51-17-4-A4-CL3_1	180	PRT
51-2-3-F10-CL1_5	181	PRT
51-2-4-F5-CL11_2	182	PRT
51-27-4-F2-CLO_2	183	PRT
51-34-3-F8-CLO_2	184	PRT
<del></del>	1	

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57-1-4-E2-CL1_2	185	PRT
57-19-2-G8-CL2_1	186	PRT
57-27-3-G10-CL2_2	187	PRT
58-33-3-B4-CL1_2	188	PRT
58-34-3-C9-CL1_2	189	PRT
58-4-4-G2-CL2_1	190	PRT
58-48-1-G3-CL2_4	191	PRT
58-6-1-H4-CL1_1	192	PRT
60-12-1-E11-CL1_2	193	PRT
65-4-4-H3-CL1_1	194	PRT
74-5-1-E4-CL1_2	195	PRT
76-13-3-A9-CL1_2	196	PRT
76-16-1-D6-CL1_1	197	PRT
76-28-3-A12-CL1_5	198	PRT
76-42-2-F3-CLO_1	199	PRT
77-16-4-G3-CL1_3	200	PRT
77-39-4-H4-CL11_4	201	PRT
78-24-3-H4-CL2_1	202	PRT
78-27-3-D1-CL1_6	203	PRT
78-28-3-D2-CLO_2	204	PRT
78-7-1-G5-CL2_6	205	PRT
84-3-1-G10-CL11_6	206	PRT
58-48-4-E2-CLO_1	207	PRT
23-12-2-G6-CL1_2	208	PRT
25-8-4-B12-CLO_5	209	PRT
26-44-3-C5-CL2_1	210	PRT
27-1-2-B3-CLO_3	211	PRT
30-12-3-G5-CLO_1	212	PRT
33-106-2-F10-CL1_3	213	PRT
33-28-4-D1-CLO_1	214	PRT
33-31-3-C8-CL2_1	215	PRT
48-24-1-D2-CL3_2	216	PRT
48-46-4-A11-CL1_4	217	PRT
51-1-4-C1-CL0_2	218	PRT
51-39-3-H2-CL1_2	219	PRT
51-42-3-F9-CL1_1	220	PRT
51-5-3-G2-CLO_4	221	PRT

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57-18-4-H5-CL2_1	222	PRT
76-23-3-G8-CL1_1	223	PRT
76-23-3-G8-CL1_3	224	PRT
78-8-3-E6-CLO_1	225	PRT
19-10-1-C2-CL1_3	226	PRT
33-11-1-B11-CL1_2	227	PRT
33-113-2-B8-CL1_2	228	PRT
33-19-1-C11-CL1_1	229	PRT
33-61-2-F6-CLO_2	230	PRT
47-4-4-C6-CL2_2	231	PRT
48-54-1-G9-CL1_1	232	PRT
51-43-3-G3-CL0_1	233	PRT
55-1-3-D11-CLO_1	234	PRT
58-14-2-D3-CL1_2	235	PRT
58-35-2-B6-CL2_3	236	PRT
76-18-1-F6-CL1_1	237	PRT
76-23-3-G8-CL2_2	238	PRT
76-30-3-B7-CL1_1	239	PRT
78-21-3-G7-CL2_1	240	PRT
58-45-4-B11-CL13_2	241	PRT
20-6-1-D11-FL2	242	DNA
20-8-4-A11-FL2	243	DNA
22-6-2-C1-FL2	244	DNA
22-11-2-H9-FL1	245	DNA
23-8-3-B1-FL1	246	DNA
24-3-3-C6-FL1	247	DNA
24-4-1-H3-FL1	248	DNA
26-45-2-C4-FL2	249	DNA
26-48-1-H10-FL1	250	DNA
26-49-1-A5-FL2	251	DNA
30-6-4-E3-FL3	252	DNA
33-6-1- <b>G</b> 11- <b>FL</b> 1	253	DNA
33-8-1-A3-FL2	254	DNA
33-11-3-C6-FL1	255	DNA
33-14-4-E1-FL1	256	DNA
33-21-2-D5-FL1	257	DNA
33-26-4-E10-FL1	258	DNA

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33-27-1-E11-FL1	259	DNA
33-28-4-D1-FL1	260	DNA
33-28-4-E2-FL2	261	DNA
33-30-4-C4-FL1	262	DNA
33-35-4-F4-FL1	263	DNA
33-36-3-F2-FL2	264	DNA
33-52-4-F9-FL2	265	DNA
33-52-4-H3-FL1	266	DNA
33-59-1-B7-FL1	267	DNA
33-71-1-A8-FL1	268	DNA
33-72-2-B2-FL1	269	DNA
33-105-2-C3-FL1	270	DNA
33-107-4-C3-FL1	271	DNA
33-110-2-G4-FL1	272	DNA
47-7-4-D2-FL2	273	DNA
47-10-2-G12-FL1	274	DNA
47-14-3-D8-FL1	275	DNA
47-18-3-C2-FL1	276	DNA
47-18-3-G5-FL2	277	DNA
47-18-4-E3-FL2	278	DNA
48-3-1-H9-FL3	279	DNA
48-4-2-H3-FL1	280	DNA
48-6-1-C9-FL1	281	DNA
48-7-4-H2-FL2	282	DNA
48-8-1-D8-FL3	283	DNA
48-13-3-H8-FL1	284	DNA
48-19-3-A7-FL1	285	DNA
48-19-3-G1-FL1	286	DNA
48-25-4-D8-FL1	287	DNA
48-21-4-H4-FL1	288	DNA
48-26-3-B8-FL2	289	DNA
48-29-1-E2-FL1	290	DNA
48-31-3-F7-FL1	291	DNA
48-47-3-A5-FL1	292	DNA
51-1-1- <b>G</b> 12-FL1	293	DNA
51-1-4-E9-FL3	294	DNA
51-1-4-E9-FL2		

F4 04 F40 F14	700	DALA
51-2-1-E10-FL1	296	DNA
51-2-3-F10-FL1	297	DNA
51-2-4-F5-FL1	298	DNA
51-3-3-B10-FL2	299	DNA
51-3-3-B10-FL3	300	DNA
51-7-3-G3-FL1	301	DNA
51-10-3-D11-FL1	302	DNA
51-11-3-D5-FL1	303	DNA
51-13-1-F7-FL3	304	DNA
51-15-4-H10-FL1	305	DNA
51-17-4-A4-FL1	306	DNA
51-18-1-C3-FL1	307	DNA
51-25-3-F3-FL1	308	DNA
51-27-1-E8-FL1	309	DNA
51-28-2-G1-FL2	310	DNA
51-39-3-H2-FL1	311	DNA
51-42-3-F9-FL1	312	DNA
51-44-4-H4-FL1	313	DNA
55-1-3-H10-FL1	314	DNA
55-5-4-A6-FL1	315	DNA
58-26-3-D1-FL1	316	DNA
57-18-1-D5-FL1	317	DNA
57-27-3-A11-FL1	318	DNA
57-27-3-G10-FL2	319	DNA
58-10-3-012-FL1	320	DNA
58-11-1-G10-FL1	321	DNA
58-11-2-G8-FL2	322	DNA
58-36-3-A9-FL2	323	DNA
58-38-1-A2-FL2	324	DNA
58-38-1-E5-FL1	325	DNA
58-44-2-B3-FL3	326	DNA
58-45-3-H11-FL1	327	DNA
58-53-2-B12-FL2	328	DNA
59-9-4-A10-FL1	329	DNA
60-16-3- <b>A6-FL</b> 1	330	DNA
60-17-3-G8-FL2	331	DNA
62-5-4-B10-FL1	332	DNA
L	<u> </u>	

	• (	
65-4-4-H3-FL1	333	DNA
74-3-1-B9-FL1	334	DNA
76-4-1- <b>G</b> 5-FL1	335	DNA
76-7-3-A12-FL1	336	DNA
76-16-4-C9-FL3	337	DNA
76-30-3-B7-FL1	338	DNA
77-5-1-C2-FL1	339	DNA
77-5-4-E7-FL1	340	DNA
77-11-1-A3-FL1	341	DNA
77-16-3-D7-FL1	342	DNA
77-16-4-G3-FL1	343	DNA
77-25-1-A6-FL1	344	DNA
77-26-2-F2-FL3	345	DNA
78-6-2-E3-FL2	346	DNA
78-7-1-G5-FL2	347	DNA
78-16-2-C2-FL1	348	DNA
78-18-3-B4-FL3	349	DNA
78-20-1-G11-FL1	350	DNA
78-22-3-E10-FL1	351	DNA
78-24-2-B8-FL1	352	DNA
78-24-3-A8-FL1	353	DNA
78-24-3-H4-FL2	354	DNA
78-25-1-F11-FL1	355	DNA
78-26-1-B5-FL1	356	DNA
78-27-3-D1-FL1	357	DNA
78-29-1-B2-FL1	358	DNA
78-29-4-B6-FL1	359	DNA
14-1-3-E6-FL1	360	DNA
30-9-1-G8-FL2	361	DNA
33-10-4-H2-FL2	362	DNA
33-10-4-H2-FL1	363	DNA
74-10-3-C9-FL2	364	DNA
33-97-4- <b>G</b> 8-FL3	365	DNA
33-97-4- <b>G</b> 8-FL2	366	DNA
33-104-4-H4-FL1	367	DNA
47-2-3-B3-FL1	368	DNA
47-37-4-G11-FL1	369	DNA

57-25-1-F10-FL2	370	DNA
58-19-3-03-FL1	371	DNA
58-34-3-C9-FL2	372	DNA
58-48-4-E2-FL2	373	DNA
76-21-1-C4-FL1	374	DNA
78-26-2-H7-FL1	375	DNA
77-20-2-E11-FL1	376	DNA
47-1-3-F7-FL2	377	DNA
20-6-1-D11-FL2	378	PRT
20-8-4-A11-FL2	379	PRT
22-6-2-C1-FL2	380	PRT
22-11-2-H9-FL1	381	PRT
23-8-3-B1-FL1	382	PRT
24-3-3-C6-FL1	383	PRT
24-4-1-H3-FL1	384	PRT
26-45-2-C4-FL2	385	PRT
26-48-1-H10-FL1	386	PRT
26-49-1-A5-FL2	387	PRT
30-6-4-E3-FL3	388	PRT
33-6-1- <b>G</b> 11- <b>F</b> L1	389	PRT
33-8-1-A3-FL2	390	PRT
33-11-3-C6-FL1	391	PRT
33-14-4-E1-FL1	392	PRT
33-21-2-D5-FL1	393	PRT
33-26-4-E10-FL1	394	PRT
33-27-1-E11-FL1	395	PRT
33-28-4-D1-FL1	396	PRT
33-28-4-E2-FL2	397	PRT
33-30-4-C4-FL1	398	PRT
33-35-4-F4-FL1	399	PRT
33-36-3-F2-FL2	400	PRT
33-52-4-F9-FL2	401	PRT
33-52-4-H3-FL1	402	PRT
33-59-1-B7-FL1	403	PRT
33-71-1-A8-FL1	404	PRT
33-72-2-B2-FL1	405	PRT
33-105-2-C3-FL1	406	PRT

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33-107-4-C3-FL1	407	PRT
33-110-2-G4-FL1	408	PRT
47-7-4-D2-FL2	409	PRT
47-10-2-G12-FL1	410	PRT
47-14-3-D8-FL1	411	PRT
47-18-3-C2-FL1	412	PRT
47-18-3-G5-FL2	413	PRT
47-18-4-E3-FL2	414	PRT
48-3-1-H9-FL3	415	PRT
48-4-2-H3-FL1	416	PRT
48-6-1- <b>C9</b> -FL1	417	PRT
48-7-4-H2-FL2	418	PRT
48-8-1-D8-FL3	419	PRT
48-13-3-H8-FL1	420	PRT
48-19-3-A7-FL1	421	PRT
48-19-3-G1-FL1	422	PRT
48-25-4-D8-FL1	423	PRT
48-21-4-H4-FL1	424	PRT
48-26-3-B8-FL2	48-26-3-B8-FL2 425	
48-29-1-E2-FL1	-E2-FL1 426	
48-31-3-F7-FL1	427	PRT
48-47-3-A5-FL1	428	PRT
51-1-1-G12-FL1	429	PRT
51-1-4-E9-FL3	430	PRT
51-1-4-E9-FL2	431	PRT
51-2-1-E10-FL1	432	PRT
51-2-3-F10-FL1	51-2-3-F10-FL1 433 PR	
51-2-4-F5-FL1	51-2-4-F5-FL1 434	
51-3-3-B10-FL2	435	PRT
51-3-3-B10-FL3	436	PRT
51-7-3-G3-FL1	437	PRT
51-10-3-D11-FL1	438	PRT
51-11-3-D5-FL1	439	PRT
51-13-1-F7-FL3	440	PRT
51-15-4-H10-FL1	441	PRT
51-17-4-A4-FL1	442	PRT
51-18-1-C3-FL1	443	PRT

		107.	
51-25-3-F3-FL1	444	PRT	
51-27-1-E8-FL1	445	PRT	
51-28-2-G1-FL2	446	PRT	
51-39-3-H2-FL1	447	PRT	
51-42-3-F9-FL1	448	PRT	
51-44-4-H4-FL1	449	PRT	
55-1-3-H10-FL1	450	PRT	
55-5-4-A6-FL1	451	PRT	
58-26-3-D1-FL1	452	PRT	
57-18-1-D5-FL1	453	PRT	
57-27-3-A11-FL1	454	PRT	
57-27-3-G10-FL2	455	PRT	
58-10-3-D12-FL1	456	PRT	
58-11-1-G10-FL1	457	PRT	
58-11-2-G8-FL2	458	PRT	
58-36-3-A9-FL2	459	PRT	
58-38-1-A2-FL2	460	PRT	
58-38-1-E5-FL1	461	PRT	
58-44-2-B3-FL3	462	PRT	
58-45-3-H11-FL1	463	PRT	
58-53-2-B12-FL2	464	PRT	
59-9-4-A 10-FL1	465	PRT	
60-16-3-A6-FL1	466	PRT	
60-17-3-G8-FL2	467	PRT	
62-5-4-B10-FL1	468	PRT	
65-4-4-H3-FL1	25 4 4 112 51 4		
74-3-1-B9-FL1			
76-4-1-G5-FL1	471	PRT	
76-7-3-A12-FL1	472	PRT	
76-16-4-C9-FL3	473	PRT	
76-30-3- <b>B</b> 7-FL1	474	PRT	
77-5-1-C2-FL1	475	PRT	
77-5-4-E7-FL1	476	PRT	
77-11- <b>1-A3-FL</b> 1	477	PRT	
77-16-3-D7-FL1	478	PRT	
77-16-4-G3-FL1	479	PRT	
77-25-1-A6-FL1	480	PRT	

77-26-2-F2-FL3	481	PRT
78-6-2-E3-FL2	482	PRT
78-7-1-G5-FL2	483	PRT
78-16-2-C2-FL1	484	PRT
78-18-3-B4-FL3	485	PRT
78-20-1-G11-FL1	486	PRT
78-22-3-E10-FL1	487	PRT
78-24-2-B8-FL1	488	PRT
78-24-3-A8-FL1	489	PRT
78-24-3-H4-FL2	490	PRT
78-25-1-F11-FL1	491	PRT
78-26-1-B5-FL1	492	PRT
78-27-3-D1-FL1	493	PRT
78-29-1-B2-FL1	494	PRT
78-29-4-B6-FL1	495	PRT
14-1-3-E6-FL1	496	PRT
30-9-1-G8-FL2	497	PRT
33-10-4-H2-FL2	498	PRT
33-10-4-H2-FL1	499	PRT
74-10-3-C9-FL2	500	PRT
33-97-4-G8-FL3	501	PRT
33-97-4-G8-FL2	502	PRT
33-104-4-H4-FL1	503	PRT
47-2-3-B3-FL1	504	PRT
47-37-4-G11-FL1	505	PRT
57-25-1-F10-FL2	506	PRT
58-19-3-D3-FL1	507	PRT
58-34-3-C9-FL2	508	PRT
58-48-4-E2-FL2	509	PRT
76-21-1- <b>C4</b> -FL1	510	PRT
78-26-2-H7-FL1	511	PRT
77-20-2-E11-FL1	512	PRT
47-1-3-F7-FL2	513	PRT
4/-1-3-F7-FL2	513	PRT

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## TABLE VIII

ID	Locations	PROSITE Signature Name
195	110-121	Aldehyde dehydrogenases csyteine active site
221	28-37	ATP synthase alpha and beta subunits signature
223	171-181	Regulator of chromosome condensation (RCC1) signature 2
225	90-112	Phosphatidylethanolamine-binding protein family signature
226	10-34	Protein kinases ATP-binding region signature

## WHAT IS CLAIMED IS:

- 1. A purified or isolated nucleic acid comprising the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary thereto.
- 2. A purified or isolated nucleic acid comprising at least 10 consecutive bases of the sequence of one of SEO ID NOs: 40-140 and 242-377 or one of the sequences complementary thereto.
  - 3. A purified or isolated nucleic acid comprising the full coding sequences of one of SEQ ID NOs: 40, 42-44, 46, 48, 49, 51, 53, 60, 62-72, 76-78, 80-83, 85-88, 90, 93, 94, 97, 99-102, 104, 107-125, 127, 132, 135-138, 140 and 242-377 wherein the full coding sequence comprises the sequence encoding signal peptide and the sequence encoding mature protein.
- A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40-44, 46, 48, 49, 51-53, 55, 56, 58-72, 75-78, 80-88, 90, 93, 94, 97, 99-125, 127, 132, 133, 135-138, 140, and 242-377 which encode a mature protein.
- A purified or isolated nucleic acid comprising the nucleotides of one of SEQ ID NOs: 40, 42-46, 48,
   49, 51, 53, 57, 60, 62-73, 76-78, 80-83, 85-88, 90, 93-95, 97, 99-102, 104, 107-125, 127, 128, 130, 132, 134-140
   and 242-377 which encode the signal peptide.
  - 6. A purified or isolated nucleic acid encoding a polypeptide having the sequence of one of the sequences of SEO ID Nos: 141-241 and 378-513.
- 7. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a mature protein included in one of the sequences of SEO ID Nos: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-20 189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
  - 8. A purified or isolated nucleic acid encoding a polypeptide having the sequence of a signal peptide included in one of the sequences of SEO ID Nos: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
    - A purified or isolated protein comprising the sequence of one of SEO ID NOs: 141-241 and 378-513.
- 10. A purified or isolated polypeptide comprising at least 10 consecutive amino acids of one of the sequences of SEQ ID NOs: 141-241 and 378-513.
  - 11. An isolated or purified polypeptide comprising a signal peptide of one of the polypeptides of SEQ ID NOs: 141, 143-147, 149, 150, 152, 154, 158, 161, 163-174, 177-179, 181-184, 186-189, 191, 194-196, 198, 200-203, 205, 208-226, 228, 229, 231, 233, 235-241, and 378-513.
- 30 12. An isolated or purified polypeptide comprising a mature protein of one of the polypeptides of SEO IO NOs: 141-145, 147, 149, 150, 152-154, 156, 157, 159-172, 176-179, 181-189, 191, 194, 195, 198, 200-226, 228, 233, 234, 236-239, 241 and 378-513.
  - 13. A method of making a protein comprising one of the sequences of SEQ ID NO: 141-241 and 378-513, comprising the steps of:

cDNA.

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obtaining a cDNA comprising one of the sequences of sequence of SEO ID NO: 40-140 and 242-377; inserting said cDNA in an expression vector such that said cDNA is operably linked to a promoter; and introducing said expression vector into a host cell whereby said host cell produces the protein encoded by said

- The method of Claim 13, further comprising the step of isolating said protein.
  - 15. A protein obtainable by the method of Claim 14.
  - A host cell containing a recombinant nucleic acid of Claim 1.
- 17. A purified or isolated antibody capable of specifically binding to a protein having the sequence of one of SEO ID NOs: 141-241 and 378-513.
- 10 18. In an array of polynucleotides of at least 15 nucleotides in length, the improvement comprising inclusion in said array of at least one of the sequences of SEQ ID NOs: 40-140 and 242-377, or one of the sequences complementary to the sequences of SEQ ID NOs: 40-140 and 242-377, or a fragment thereof of at least 15 consecutive nucleotides.
- 19. A purified or isolated nucleic acid of at least 15 bases capable of hybridizing under stringent conditions to the sequence of one of SEQ ID NOs: 40-140 and 242-377 or a sequence complementary to one of the sequences of SEQ ID NOs: 40-140 and 242-377.
  - 20. A purified or isolated antibody capable of binding to a polypeptide comprising at least 10 consecutive amino acids of the sequence of one of SEQ ID NDs: 141-241 and 378-513.

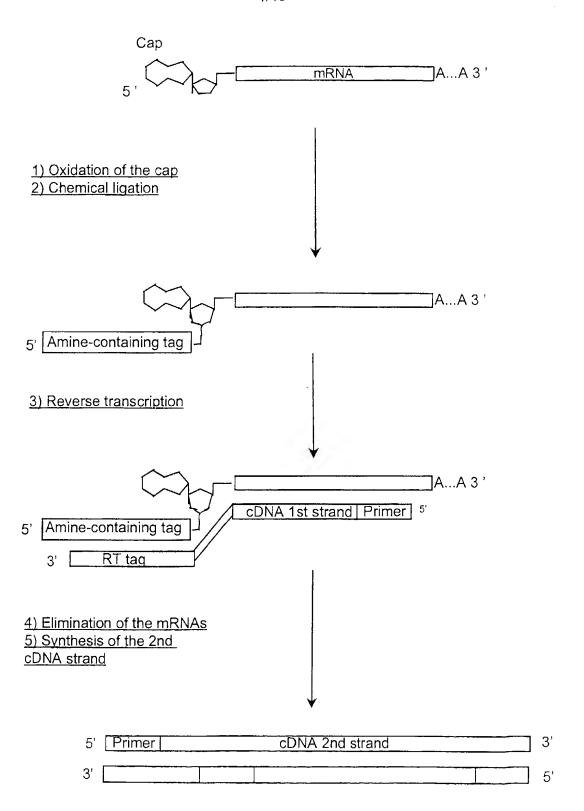
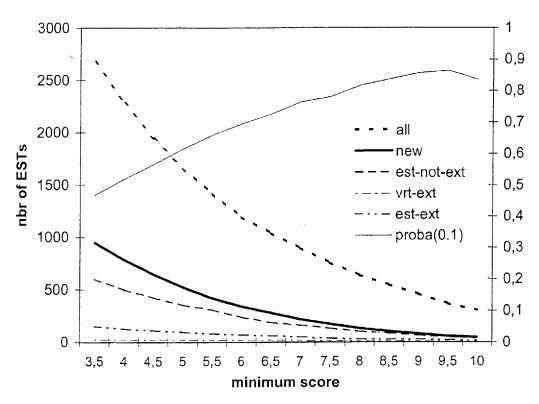


Figure 1

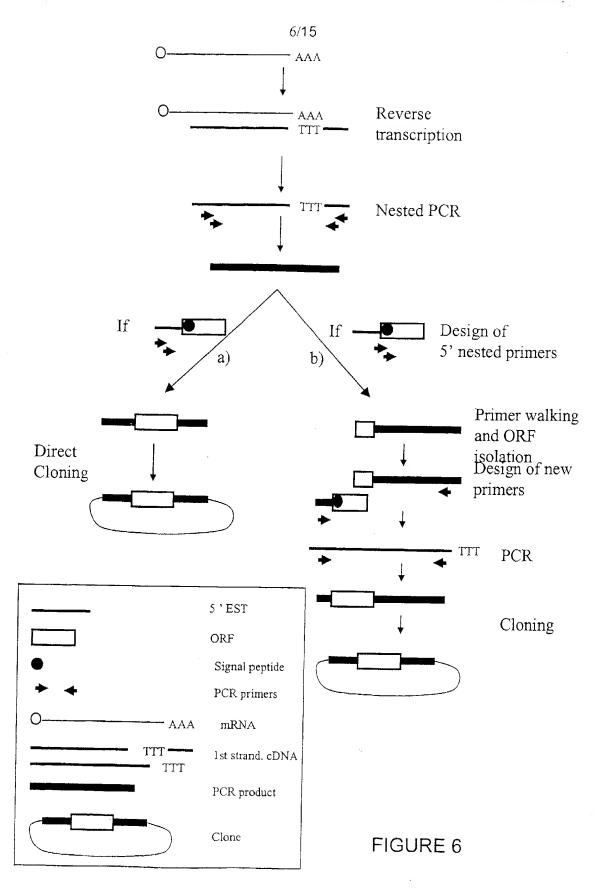
Minimum signal peptide score	false positive rate	false negative rate	proba(0.1)	proba(0.2)
3,5	0,121	0,036	0,467	0,664
4	0,096	0,06	0,519	0,708
4,5	0,078	0,079	0,565	0,745
5	0,062	0,098	0,615	0,782
5,5	0,05	0,127	0,659	0,813
6	0,04	0,163	0,694	0,836
6,5	0,033	0,202	0,725	0,855
] 7	0,025	0,248	0,763	0,878
7,5	0,021	0,304	0,78	0,889
8	0,015	0,368	0,816	0,909
8,5	0,012	0,418	0,836	0,92
9	0,009	0,512	0,856	0,93
9,5	0,007	0,581	0,863	0,934
10	0,006	0,679	0,835	0,919

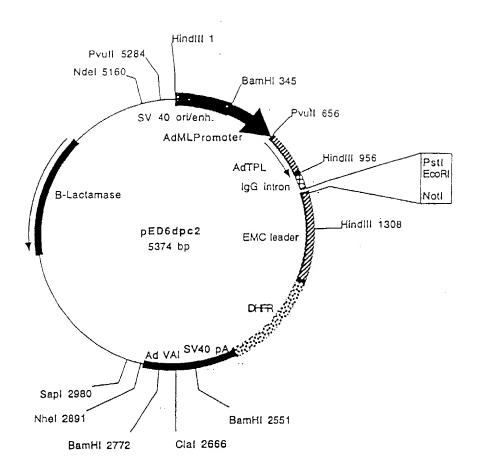
## influence of minimum score on signal peptide recognition



-		<del></del>	T		
Minimum signal peptide score	All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
3,5	2674	947	599	23	150
4	2278	784	499	23	126
4,5	1943	647	425	22	112
5	1657	523	353	21	96
5,5	1417	419	307	19	80
6	1190	340	238	18	68
6,5	1035	280	186	18	60
7	893	219	161	15	48
7,5	753	173	132	12	36
8	636	133	101	11	29
8,5	543	104	83	8	26
9	456	81	63	6	24
9,5	364	57	48	6	18
10	303	47	35	6	15

	<del></del>				
Tissue	All ESTs	New ESTs	ESTs matching public EST closer than 40 bp from beginning	ESTs extending known mRNA more than 40 bp	ESTs extending public EST more than 40 bp
Brain	329	131	75	3	24
Cancerous prostate	134	40	37	1	6
Cerebellum	17	9	1	0	6
Colon	21	11	4	0	0
Dystrophic muscle	41	18	8	0	1
Fetal brain	70	37	16	0	1
Fetal kidney	227	116	46	1	19
Fetal liver	13	7	2	0	0
Heart	30	15	7	0	1
Hypertrophic prostate	86	23	22	2	2
Kidney	10	7	3	0	0
Large intestine	21	8	4	0	1
Liver	23	9	6	0	0
Lung	24	12	4	0	1
Lung (cells)	57	38	6	0	4
Lymph ganglia	163	60	23	2	12
Lymphocytes	23	6	4	0	2
Muscle	33	16	6	0	4
Normal prostate	181	61	45	7	11
Ovary	90	57	12	1	2
Pancreas	48	11	6	0	1
Placenta	24	5	1	0	0
Prostate	34	16	4	0	2
Spleen	56	28	10	0	1
Substantia nigra	108	47	27	1	6
Surrenals	15	3	3	1	0
Testis	131	68	25	1	8
Thyroid	17	8	2	0	8 2 3
Umbilical cord	55	17	12	1	
Uterus	28	15	3	0	2
Non tissue-specific	568	48	177	2	28
Total	2677	947	601	23	150





Plasmid name: pED6dpc2 Plasmid size: 5374 bp



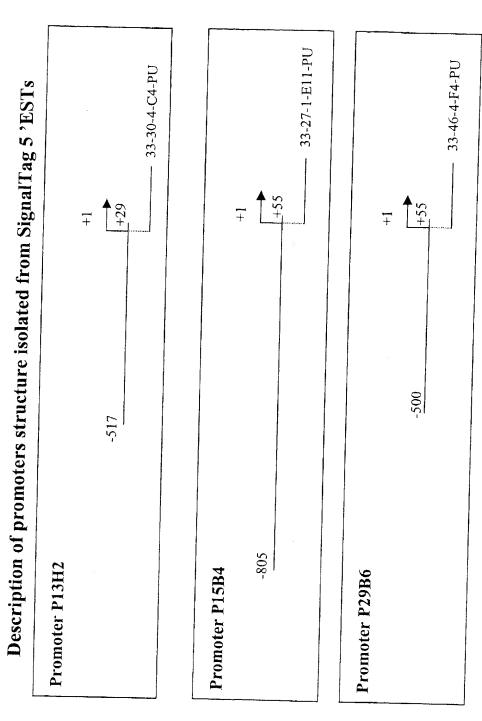


FIGURE 8

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# Description of Transcription Factor Binding Sites present on promoters isolated from SignalTag sequences

### Promoter sequence P13H2 (546 bp):

Matrix	Position	Orientation	Score	Length	Sequence
CMYB_01	-502	+	0.983	9	TGTCAGTTG
MYOD_Q6	-501	-	0.961	10	CCCAACTGAC
S8_01	-444	-	0.960	11	AATAGAATTAG
S8_01	-425	+	0.966	11	AACTAAATTAG
DELTAEF1_01	-390	•	0.960	11	GCACACCTCAG
GATA_C	-364		0.964	11	AGATAAATCCA
CMYB_01	-349	+	0.958	9	CTTCAGTTG
GATA1_02	-343	+	0.959	14	TTGTAGATAGGACA
GATA_C	-339	+	0.953	11	AGATAGGACAT
TAL1ALPHAE47_01	-235	+	0.973	16	CATAACAGATGGTAAG
TAL1BETAE47_01	-235	+	0.983	16	CATAACAGATGGTAAG
TAL1BETAITF2_01	-235	+	0.978	16	CATAACAGATGGTAAG
MYOD_Q6	-232	-	0.954	10	ACCATCTGTT
GATA1_04	-217	-	0.953	13	TCAAGATAAAGTA
IK1_01	-126	+	0.963	13	AGTTGGGAATTCC
IK2_01	-126	+	0.985	12	AGTTGGGAATTC
CREL_01	-123	+	0.962	10	TGGGAATTCC
GATA1_02	-96	+	0.950	14	TCAGTGATATGGCA
SRY_02	-41	-	0.951	12	TAAAACAAAACA
E2F_02	-33	+	0.957	8	TTTAGCGC
MZF1_01	-5	-	0.975	8	TGAGGGGA

#### Promoter sequence P15B4 (861bp):

Matrix	Position	Orientation	Score	Length	Sequence
NFY_Q6	<b>-</b> 748	-	0.956	11	GGACCAATCAT
MZF1_01	<b>-</b> 738	+	0.962	8	CCTGGGGA
CMYB_01	-684	+	0.994	9	TGACCGTTG
VMYB_02	-682	-	0.985	9	TCCAACGGT
STAT_01	-673	+	0.968	9	TTCCTGGAA
STAT_01	-673	-	0.951	9	TTCCAGGAA
MZF1_01	-556	-	0.956	8	TTGGGGGA
IK2_01	-451	+	0.965	12	GAATGGGATTTC
MZF1_01	-424	+	0.986	8	AGAGGGGA
SRY_02	-398	-	0.955	12	GAAAACAAAACA
MZF1_01	-216	+	0.960	8	GAAGGGGA
MYOD_Q6	-190	+	0.981	10	AGCATCTGCC
DELTAEF1_01	-176	+	0.958	11	TCCCACCTTCC
S8_01	5	-	0.992	11	GAGGCAATTAT
MZF1_01	16	-	0.986	8	AGAGGGGA

## Promoter sequence P29B6 (555 bp):

Matrix	Position Ori	ientation	Score	Length	Sequence
ARNT_01	-311	+	0.964	16	GGACTCACGTGCTGCT
NMYC_01	-309	+	0.965	12	ACTCACGTGCTG
USF_01	-309	+	0.985	12	ACTCACGTGCTG
USF_01	-309	-	0.985	12	CAGCACGTGAGT
NMYC_01	-309	-	0.956	12	CAGCACGTGAGT
MYCMAX_02	-309	-	0.972	12	CAGCACGTGAGT
USF_C	-307	+	0.997	8	TCACGTGC
USF_C	-307	-	0.991	8	GCACGTGA
MZF1_01	-292	-	0.968	8	CATGGGGA
ELK1_02	-105	+	0.963	14	CTCTCCGGAAGCCT
CETS1P54_01	-102	+	0.974	10	TCCGGAAGCC
AP1_Q4	-42	-	0.963	11	AGTGACTGAAC
AP1FJ_Q2	-42	-	0.961	11	AGTGACTGAAC
PADS_C	45	+	1.000	9	TGTGGTCTC

Figure 9

#### 10/15

100.0% identity in 125 aa overlap 20 10 30 40 50 SEQ ID NO: 217 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA SEQ ID NO: 516 MADEELEALRRQRLAELQAKHGDPGDAAQQEAKHREAEMRNSILAQVLDQSARARLSNLA 10 20 30 40 50 70 80 90 100 110 120 SEQ ID NO: 217 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD SEQ ID NO: 516 LVKPEKTKAVENYLIQMARYGQLSEKVSEQGLIEILKKVSQQTEKTTTVKFNRRKVMDSD 70 80 90 100 110 120 SEQ ID NO: 217 EDDDY ::::X SEQ ID NO: 516 EDDDY

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CLUSTAL W(1.5) multiple sequence alignment

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SEQ SEQ SEQ SEQ	ID I	NO: NO:	232 174	GNKSSVNSTVLVKNTKKTNP

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99.6% identity in 225 aa overlap SEQ ID NO: 515 PTAVQKEEARQDVEALLSRTVRTQILTGKELRVATQEKEGSSGRCMLTLLGLSFILAGLI SEQ ID NO: 231 LRVATQEKEGSSGRCMLTLLGLSFILAGLI SEQ ID NO: 515 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 231 VGGACIYKYFMPKSTIYRGEMCFFDSEDPANSLRGGEPNFLPVTEEADIREDDNIAIIDV SEQ ID NO: 515 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGNCYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 231 PVPSFSDSDPAAIIHDFEKGMTAYLDLLLGICYLMPLNTSIVMPPKNLVELFGKLASGRY SEQ ID NO: 515 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR SEQ ID NO: 231 LPQTYVVREDLVAVEEIRDVSNLGIFIYQLCNNRKSFRLRRRDLLLGFNKRAIDKCWKIR SEQ ID NO: 515 HFPNEFIVETKICQE ::::::::::::::: SEQ ID NO: 231 HFPNEFIVETKICQE

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99.7% identity in 353 aa overlap SEO ID NO:196 MERGLKSADPRDGTGYTGWAGIAVLYLHLY SEO ID NO:518 LAEGYFDAAGRLTPEFSQRLTNKIRELLQQMERGLKSADPRDGTGYTGWAGIAVLYLHLY 30 40 5.0 SEQ ID NO:196 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR SEQ ID NO:518 DVFGDPAYLQLAHGYVKQSLNCLTKRSITFLCGDAGPLAVAAVLYHKMNNEKQAEDCITR 90 100 110 120 SEO ID NO:196 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKTPQSHIQQICETILTSGENLARK SEQ ID NO:518 LIHLNKIDPHAPNEMLYGRIGYIYALLFVNKNFGVEKIPQSHIQQICETILTSGENLARK 150 160 170 SEQ ID NO:196 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF SEQ ID NO:518 RNFTAKSPLMYEWYQEYYVGAAHGLAGIYYYLMQPSLQVSQGKLHSLVKPSVDYVCQLKF 210 220 SEQ ID NO:196 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:518 PSGNYPPCIGDNRDLLVHWCHGAPGVIYMLIQAYKVFREEKYLCDAYQCADVIWQYGLLK SEQ ID NO:196 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM ...... SEQ ID NO:518 KGYGLCHGSAGNAYAFLTLYNLTQDMKYLYRACKFAEWCLEYGEHGCRTPDTPFSLFEGM 330 340 SEQ ID NO:196 AGTIYFLADLLVPTKARFPAFEL SEQ ID NO:518 AGTIYFLADLLVPTKARFPAFEL 

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98.5% identity in 194 aa overlap 120 110 SEQ ID NO:519 ARNLPPLTDAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL SEQ ID NO:158 ARNLPPLTEAQKNKLRHLSVVTLAAKVKCIPYAVLLEALALRNVRQLEDLVIEAVYADVL 60 70 В0 90 100 160 170 180 190 SEQ ID NO:519 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIAQTLQEWCVGCEVVLSGIEEQVSRANQHKEQ SEQ ID NO:158 RGSLDQRNQRLEVDYSIGRDIQRQDLSAIARTLQEWCVGCEVVLSGIEEQVSRANQHKEQ 120 130 140 150 160 210 220 230 240 250 SEQ ID NO:519 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPASGTNQRQPSKKASKG SEQ ID NO:158 QLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQHLTELREPAPGTNQRQPSKKASKG 180 190 200 210 220 270 SEQ ID NO:519 KGLRGSAKIWSKSN ::::::::::::::: SEQ ID NO:158 KGLRGSAKIWSKSN 240 250 88.7% identity in 62 aa overlap 20 30 40 50 SEQ ID NO:519 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELAESDF SEQ ID NO:158 MSAEVKVTGQNQEQFLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELXARNL 10 20 30 40 50 SEQ ID NO:519 AS SEQ ID NO:158 PP

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Ala Ala Phe Ile Phe Ser Tyr Ile Thr Ala Val Thr Leu Hi	s His Ile
1 5 10	15
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Asp Pro Ala Leu Pro Tyr Ile Ser Asp Thr Gly Thr Val Al	a Pro Xaa
20 25	30
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Lys Cys Leu Phe Gly Ala Met Leu Asn Ile Ala Ala Val Le	eu Cys Gln
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Lys	
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i i i i i i i i i i i i i i i i i i i	

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722

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Cys lie lie lie 140	Val Ala Ile Ala	Leu Leu Ile Leu		
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Gln Arg Xaa Xaa	Lys Asn Lys Glu	Pro Ser Glu Val	Asn Asn Ala Glu	580
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Pro Leu Asp Met	Lys Gly Gly His			
~~* ~~~ ~~~ ~~	190	195	200	
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Asp Giu Aig Leu 205	Ini Pio Leu			
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gcc c Ala L	eu Le	is c ctg eu Lei	cct Pro	cac His	tgc Cys	-10 cag Gln	aag Lys	ccc Pro	ttt Phe 10	gtg Val	-5 tat Tyr	gac Asp	ctt Leu	cac His 15	14	ŧ <b>4</b>
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att t Ile C	gc ct	t gat eu Asp	: ttg	aaa Lys	gat Asp	act Thr	ttc Phe 40	tgc	agt Ser	agt Ser	ctg Leu	ctt Leu 45	att	tat Tyr	24	ł C
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Gly Ala Ala Phe Tyr Pro Ile Tyr Phe Arg Pro Leu Met Arg Leu Glu
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Gln	Phe	Arg	Glu	Trp -60	Phe	Leu	Lys	Glu	Phe -55	Pro	Gln	Ile	Arg	tgg Trp -50	Lys	341
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1 5 10 15	
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Ala Thr Ala Gly Ile Ala Ser Ser Ile Val Glu Asn Thr Tyr Thr Arg	
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Leu Glu Ala Leu Arg Asp Ile Leu His Asp Ile Thr Pro Asn Val Leu	ı
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tee tit gea ett gat tit gae gaa gee aca aaa atg att geg aat gat	725
Ser Phe Ala Leu Asp Phe Asp Glu Ala Thr Lys Met Ile Ala Asn Asp	)
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ttc aca ggt cat atg ggg aag ctg gta ccc ctg aag gag acc atc aaa Phe Thr Gly His Met Gly Lys Leu Val Pro Leu Lys Glu Thr Ile Lys 35 40 45	44
gga ttc cag cag att ttg gca ggt gaa tat gac cat ctc cca gaa cag Gly Phe Gln Gln Ile Leu Ala Gly Glu Tyr Asp His Leu Pro Glu Gln 50 60	49
gcc ttc tat atg gtg gga ccc att gaa gaa gct gtg gca aaa gct gat Ala Phe Tyr Met Val Gly Pro Ile Glu Glu Ala Val Ala Lys Ala Asp 65 70 75	54
aag ctg gct gaa gag cat tca tcg tgaggggtct ttgtcctctg tactgtctct Lys Leu Ala Glu Glu His Ser Ser 80 85	59
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Cay	Cla	Lou	990	Tou	Lve	Cln	Gln	Tla	Glu	Ser	Glu	Val	Δla	Asn	Leu		
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gettttaaet tettetttga tetaaggatt acctaettgt taattteeaa atattatett	420
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ggct atg teg eeg agg etg gag tge agt ggt gea ate ttg get eac tge	529
Met Ser Pro Arg Leu Glu Cys Ser Gly Ala Ile Leu Ala His Cys	
1 5 10 15	
aac ccc cgc ctc cca ggt tca agt tat tct cct gcc tca gct act tgg	577
Asn Pro Arg Leu Pro Gly Ser Ser Tyr Ser Pro Ala Ser Ala Thr Trp	
20 25 30	

25

626

682

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Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala Glu
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Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly Val
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                    -20
tgt cca aca tgg caa tgg gct aca ggg gaa gaa ttg aaa gtg aag gca
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Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys Ala
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Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro Cys
tat aag cgg tgc aaa cag atg gaa tat tca gat gaa ttg gaa gct atc
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Tyr Lys Arg Cys Lys Gln Met Glu Tyr Ser Asp Glu Leu Glu Ala Ile
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Ile Glu Glu Asp Asp Gly Asp Gly Gly Trp Val Asp Thr Tyr His Asn
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Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg Lys
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cct tta aca gtt gag cac atg tat gaa gac atc agt cag gat cat gtg
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Pro Leu Thr Val Glu His Met Tyr Glu Asp Ile Ser Gln Asp His Val
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Lys Lys Thr Val Thr Ile Glu Asn His Pro His Leu Pro Pro Pro
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Leu Leu Ile Phe Leu Lys Phe Val Gln Ala Val Ile Pro Thr Ile Glu
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Tyr Asp Tyr Thr Arg His Phe Thr Met
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agc tgc tca gac ctg ctt ccc tgg gag gtg acg gaa cca gca ctg Ser Cys Ser Asp Leu Leu Pro Trp Glu Gly Val Thr Glu Pro Ala Leu -45 -40 -35	803												
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acc tot gaa coc oto aca goo tagggacagg ageggeegge ttacetggtg Thr Ser Glu Pro Leu Thr Ala 80	341												
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tctgtggaac tttt cgaaacaatc tatg	tttatt to	gtagaagga	gcaagaatat	actecacetg tgacettact agttaac	tacttgttat atatagcaca	461 521 568
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			-33		- 20	
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Tyr Gln Gly Tyr -25 gtt gca ctt gct Val Ala Leu Ala -10 ata gga gta tgc Ile Gly Val Cys	ggt ctc Gly Leu cag agt	Ala Asn  ttg gga Leu Gly -5 aaa ttc	tct aga ttt Ser Arg Phe -20 ttt ggc ctt Phe Gly Leu cat ttt ttt	e Gly Ser Le -1 gga aag gt Gly Lys Va 1 gaa gat ca	g ccc aaa nu Pro Lys 5 a tca tac 11 Ser Tyr	
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Tyr Gln Gly Tyr -25 gtt gca ctt gct Val Ala Leu Ala -10 ata gga gta tgc Ile Gly Val Cys 5 ggg gct ggt ttt Gly Ala Gly Pho gag gaa tgc aaa Glu Glu Cys Lys	ggt ctc Gly Leu cag agt Gln Ser 10 ggt cca Gly Pro 25 ata aag	ttg gga Leu Gly -5 aaa ttc Lys Phe cag cat Gln His	tct aga ttt Ser Arg Phe -20 ttt ggc ctt Phe Gly Lev cat ttt ttt His Phe Phe 15 aac agg cac Asn Arg His 30 tta agt gag	gga aag gt gga aag gt Gly Lys Va gaa gat ca Glu Asp Gl tgc ctc ct Cys Leu Le	g ccc aaa nu Pro Lys 5 a tca tac cl Ser Tyr ng ctc cgt n Leu Arg 20 ct acc tgt cu Thr Cys 35 ac tct cag sp Ser Gln	270 318
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ccc tac acc cag ggc aag tgg gaa ggg gag ctg ggc acc gac ctg gta
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Pro Tyr Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu Val
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age atc ccc cat ggc ccc aac gtc act gtg cgt gcc aac att gct gcc
Ser Ile Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala Ala
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atc act gaa toa gac aag tto tto atc aac ggc too aac tgg gaa ggc
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Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu Gly
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atc ctg ggg ctg gcc tat gct gag att gcc agg cct gac gac tcc ccg
Ile Leu Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp Ser Pro
                            70
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Glu Pro Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro Asn Leu
                                           90
                        85
tto too ctg cag ctt tgt ggt got ggc tto ccc ctc aac cag tot gaa
                                                                      387
Phe Ser Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser Glu
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                   100
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Val Leu Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile Asp His
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Ser Leu Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu Trp
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Tyr Tyr Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln Asp Leu
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Lys Met Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp Ser
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                                                                      627
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Gly Thr Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala Val
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Lys Ser Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp Gly Phe
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Trp Leu Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr Pro Trp
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Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser
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tha cot tit gig agt tha ggt tig atg tgc tit ggg get tig atc gga	206
Leu Pro Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu IIe Gly	
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Leu Cys Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly	
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Ile Leu His Leu Leu Ala Gly Leu Cys Thr Leu Gly Ser Val Ser Cys	
15 20 25	350
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Tyr Val Ala Gly Ile Glu Leu Leu His Gln Lys Leu Glu Leu Pro Asp	
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ttg gtc aac atc ttc tgg ttc tac cga gag gcc ttc ctt gtc cca gcc Leu Val Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala -40 -35 -30	206
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age ege aac cet gag gtg eee ttt gag age agt gee tae ege ate tea	145

Ser					**- 1	Dro	Dhe	Glu	Ser	Ser	Ala	Tyr	Arg	Ile	Ser	
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		qcc	cgc	ggc	aag	gag	ctg	cgc	ctg	ata	ctg	agc	CCL	ctg	Dro	173
gct Ala	ser	Āla	Arg	Gly	Lys	Glu	Leu	Arg	Leu	110	Leu	ser	Pro	ьeu	-5	
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gcc	cac	ctg	cgc	ttt	tac	acg	gcc	ccg	CCT	gge	Dro	Ara	Leu	Ala	Leu	
Ala	His	Leu	Arg	Phe	Tyr	Thr	Ala	Pro	Pro	СТУ	40	Arg	ПСи	1114		
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Cys	Phe	Val	Asp	Ile	Arg	Arg	Pne	СТУ	Arg	55	Asp	<u></u>	0-7	1	60	
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tgg	cag	ccg	ggc	cgc	999	ccc	tgt	yec	Ley	Gln	Glu	Tyr	Gln	Gln	Phe	
Trp	Gln	Pro	Gly	Arg	Gly	Pro	Cys	vai	70	GIII	010	1-		75		
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agg	gag	aat	gtg	cta	cga	aac	Ton	. שכש	Acr	Livs	Ala	Phe	Asp	Arg	Pro	
Arg	Glu	Asr		. Leu	Arg	ASII	. шеи	85		-,-		_	90	_		
			80			~~~		. ago	tto	tto	aat	. qqc	att	ggc	aac Asn	529
atc	tgo	gag	y gad	CTC	Tou	yac Ner	Glr	λro	Phe	Phe	Asr	ı Gly	, Ile	Gly	Asn	
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tat	ctg	g cgg	g 90a	. gas	, alc	Let	י דעז יו דעז	Arc	Lev	Lys	Ile	e Pro	Pro	Phe	Glu	
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aag	ge	cg.	J 000	y yu	Lei	ı Glı	ı Ala	ı Lei	Gli	ı Glı	h Hi:	s Arg	g Pro	Ser		
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gaç	, To	y ac	r T.e	n Se.	r Gli	LVS	s Ile	e Ar	g Th:	r Ly	s Le	u Gl	n Ası		-	
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	- a+	~ ~=	a ct			e te	a qt	g cc	c aa	g ga	a gt	g gt	c ca	g tt	g ggt u Gly	721
To	, To	y ga	9 00 11 T.E	11 CV:	s Hi:	s Se	r Va	l Pr	о Ly	s Gl	u Va	l Va	l Gl	n Le	u Gly	
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a a		c aa	= 03	t aa	c ag	c aa	c ct	c tg	c tt	c ag	c aa	a tg	attg	tgta		/0/
GI:	ו אל נו	a Iv	s As	p Gl	y Se	r As	n Le	u Cy	s Ph	e Se	r Ly	S				
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2.0	ccta			tato	ccc	ctct	ggac	ct g	attc	accg	a tt	tgga	agtt	tgt	agcccta ggcgcag	887
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WO 99/31236 -48- PCT/IB98/02122 -

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Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu

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act	+ + c c	י אמר	240	cga	agg	aca	aac	245 aga	. gac	ctt	cct	aag	250 agg	act	gca	1009
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ga	g <b>g</b> gs	g ac	c tca r Sei	305 a gcc	; : tct	taq			310	)				312	<b>)</b>	1201
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Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe His Arg Arg Ser Leu
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Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly Val Ser Leu Pro Gly
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Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln Ser Cys Gln Met Asn
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Asn Leu Pro His Leu Gln Val Val Gly Leu Thr Trp Gly His Ile Ser
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Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile Ile Leu Ala Ser Asp
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Val Phe Phe Glu Pro Glu Asp Phe Glu Asp Ile Leu Ala Thr Ile Tyr
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Phe Leu Met His Lys Asn Pro Lys Val Gln Leu Trp Ser Thr Tyr Gln
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Met Lys Cys Val His Ile Pro Leu Glu Ser Phe Asp Ala Asp Lys Glu
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Asp Ile Ala Glu Ser Thr Leu Pro Gly Arg His Thr Val Glu Met Leu
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Val Ile Ser Phe Ala Lys Asp Ser Leu
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ctt cca Leu Pro -13!	Glu	Glu	Pro	Lys	GIu -130	Leu )	met	vai	HIS	-125	5 5	Gry	200		
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Asj	p Gl -5	у S 5	er	Ile	Met	Let	Glr -50	gly	Va	l Ar	g G			Asp	Gly	Gly	y Asn		
tac		-	ac	agt	atc	cac				~ ~+	~ ~!		45				c att		
TVI	r Th	rc	'vs	Ser	Tle	Hie	Len	999	aa.	o cu	9 91	-9 [	CC	aag	aaa	aco	att	685	
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Gly	r Il	e V	al (	Cvs	Ala	Thr	Tle	T.eu	To	Ta	c cc	. L 9	- 7	t tug	ata		ılle	829	
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Met Leu Xaa Gly Asp His Arg Ala Leu Leu Leu  1 5 10  aag ata tgg ctg ctt caa agg cca gag tca cag gaa gga ctt ctt cca Lys Ile Trp Leu Leu Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro  15 20 25  ggg aga tta gtg gtg atg gag agg aga gtt aaa atg acc tca tgt cct Gly Arg Leu Val Val Met Glu Arg Arg Val Lys Met Thr Ser Cys Pro  30 35 40  tct tgt cca cgg ttt tgt tgagtttca ctcttctaat gcaagggtct Ser Cys Pro Arg Phe Cys  45  cacactgtga accacttagg atgtgatcac tttcaggtgg ccaggaatgt tgaatgtctt tggctcagtt catttaaaaa agatactat ttgaaagttc tcagagttgt acatatgttt cacagtacag gatctgtaca taaaagttc tttctgaaac cattcaccaa gagccaatat ctaggcattt tcttggtagc acaaattttc ttattgctta gaaaattgtc ctcttgtaa gcttgtctt tatgctggga ggtgaccata gggctctgct tttaaaggaa ggcagaagggggggggg	101 149 197 257 317 377 437 497 557 617 677 737 797 857 917 977 1037
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Met Leu Xaa Gly Asp His Arg Ala Leu Leu Leu 1 5 10  aag ata tgg ctg ctt caa agg cca gag tca cag gaa gga ctt ctt cca Lys Ile Trp Leu Leu Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro 15 20 25  ggg aga tta gtg gtg atg gag agg agg gtt aaa atg acc tca tgt cct Gly Arg Leu Val Val Met Glu Arg Arg Val Lys Met Thr Ser Cys Pro 30 35 40  tct tgt cca cgg ttt tgt tgagttttca ctcttctaat gcaagggtct Ser Cys Pro Arg Phe Cys  45  cacactgtga accacttagg atgtgatcac tttcaggtgg ccaggaatgt tgaatgttt cacagtacag gatctgtaca taaaagttc tttcctaaac cattcaccaa gagccaatat tctggtag acaaatttc ttattgcta gaaaattgtc ttctgtttt tatgctgga acaaatttc ttattgcta gaaaattgc ctcttgtta tcttgtttt tatgctgga ggagagat aggacttctc aaaggccaga gtcacaggaa ggacttctc caggagatt taaaagac ctcattgcct tcttgtcac cacttaggat ggagttggat gagagagag ttaaaatgac ctcattgcac tcttgtcaca gggttttgttg agttttcact aaggctctt aagggctct cacttaggat ggattagg gtgatcact tcttgtcac aattgttt gattgttt aaggcttac cacttaggat ggattaggat ggatttttgt gagagagaga	101 149 197 257 317 377 437 497 557 617 677 737 797 857 917 977 1037 1097 1157 1217
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tac aac aga acc tcc aaa aga tgt gaa act tt Tyr Asn Arg Thr Ser Lys Arg Cys Glu Thr Pt 35	e Val Phe Ser Gly Cys 50
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tgt gtt gca aaa tac aaa cca ccg agg tgagag Cys Val Ala Lys Tyr Lys Pro Pro Arg 70 75	
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PCT/IB98/02122 -

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aaa tat aac ctt ttg gag ctc aag gag tct tgc atc cgg aac cag gac Lys Tyr Asn Leu Leu Glu Leu Lys Glu Ser Cys Ile Arg Asn Gln Asp 10 15 20	147
tgc gag act ggc tgc tgc caa cgt gct cca gac aat tgc gag tcg cac Cys Glu Thr Gly Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His 25 30 35	195
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teettettge tgeeteetee teeteeacet geteteetee etacecagag etetgtgtte accetgttee ecagageete caccatgagt ggagggaagt ggggagtgat tgaaataaag agetttttea atgaaaaaaa aaaaaaaaaa	448 508 542
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                                                                      112
                         Met Val Ala Leu Asn Leu Ile Leu Val Pro
                                                                      160
tgc tgc gct gct tgg tgt gac cca cgg agg atc cac tcc cag gat gac
Cys Cys Ala Ala Trp Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp
                                                                      208
gtg ccc cgt agc tct gct gct gat act ggg tct gcg atg cag cgg cgt
Val Pro Arg Ser Ser Ala Ala Asp Thr Gly Ser Ala Met Gln Arg Arg
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gag gcc tgg gct ggt tgg aga agg tca caa ccc ttc tct gtt ggt ctg
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Glu Ala Trp Ala Gly Trp Arg Arg Ser Gln Pro Phe Ser Val Gly Leu
                        35
                                                                      304
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Pro Ser Ala Glu Arg Leu Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg
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Ser Leu Val Gly Glu Gly Tyr Arg Ile Cys Asp Leu
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qaqtacaccc tttccaqqaa taatqttttq ggaaacactg aaatgaaatc ttcccagtat
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att Ile -15	gag	ctg Leu	gaa Glu	cct Pro	999 Gly -10	ctg	agc Ser	tcc Ser	agt Ser	gct Ala -5	gcc Ala	tgt Cys	aat Asn	ggg Gly	aag Lys 1	153
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ctg Leu	aca Thr	ata Ile 20	act Thr	gat Asp	gtt Val	ccc Pro	gtc Val 25	act Thr	gtt Val	tat Tyr	gca Ala	aca Thr 30	acg Thr	aga Arg	aag Lys	249
cca Pro	cct Pro 35	gca Ala	caa Gln	agc Ser	agc Ser	aag Lys 40	gaa Glu	atg Met	cat His	cct Pro	aaa Lys 45	tago	cacca	at <b>t</b>		295
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	)> 83 cacgo		ggto	cagag	gt t	atg Met	gca Ala -20	ccc Pro	cag Gln	act Thr	ctg Leu	ctg Leu -15	cct Pro	gtc Val	ctg Leu	51
gtt Val	ctc Leu -10	tgt Cys	gtg Val	ctg Leu	ctg Leu	ctg Leu -5	cag	gcc Ala	cag Gln	gga Gly	gga Gly 1	tac Tyr	cgt Arg	gac Asp	aag Lys 5	<b>9</b> 9
atg Met	agg Arg	atg Met	cag Gln	aga Arg 10	atc Ile	aag Lys	gtc Val	tgt Cys	gag Glu 15	aag Lys	cga Arg	ccc Pro	agc Ser	ata Ile 20	gat Asp	147
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cct gag att Pro Glu Ile	Asp Val Pr 45	o Ser Tyr	Leu Pro 50	Asp Leu	Pro Gly	Ile Ala 55	256
aac gac ctc Asn Asp Leu	Met Tyr Il	e Ala Asp	Leu Gly 65	Pro Gly	Ile Ala 70	Pro Ser	304
gcc cct ggc Ala Pro Gly 75	Thr Ile Pr	o Glu Leu 80	Pro Thr	Phe His	Thr Glu 85	Val Ala	352
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act Thr																
Thr	tac	tgo	: ttt	tgg	gac	ccc	ccc	cat	cgg	ggt	tca	cat	ta	cto	c tee	31
	Туз	Cys	: Phe	: Trp	Asp	Pro	Pro	His	Arg	Gly	Ser	His	s Ser	Let	ı Ser	
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Leu	Gli	His	Thr	Pro	Leu	Asp	Phe	Leu	Glu	Trp	Gly	Leu	Let	ı Arç	J	
			15					20					25			
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gtt	tcgt	tgt	agca	catt	aa a	aata	tttt	c cc	c						-	45
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gtca			accg	cccti	tt gç	gttcc	cgag									52
gtca			accg	cccti	tt gg	gttcc	cgag				Phe S	Ser 1		agc ( Ser :		52
	aggt	tgc .						N	let I	eu I	Phe S	Ser 1	Leu	Ser :	Leu	52
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ctc Leu att	tcc Ser -5	aac Asn ggc	ctt Leu caa	aac Asn tca	caa Gln gct	atc Ile 1 cag	ggc Gly ctg	agc Ser ttt	et I agc Ser att	eu I cac His 5 tac	Phe S ctc Leu caa	Ser 1 -10 gac Asp atg	cgc Arg	cca Pro tca	cac His 10 caa	100
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Thr Pro Leu								071
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	-		_site													
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Lvs	Leu	His	Ser	Leu	Val	Lys	Pro	Ser	Val	Asp	Tyr	Val	Cys	Gln	Leu	
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Phe Asp Val Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys	
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Phe .	Asn	Ile	Thr	Arg	Asp	Phe	Phe	Asp	Pro	Leu	Tyr	Pro	Gly	Thr	Lys	
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act gag atg cct cta aga gcc aaa gga gtc aac act tgagcctagg Thr Glu Met Pro Leu Arg Ala Lys Gly Val Asn Thr 10 15	304
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Met Met Trp Gln Lys Tyr Ala Gly Ser Arg Arg -30 -25	
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-30 -25 toa atg cot otg gga goa agg atc ott tto cac ggt gtg tto tat goo	161 209
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Arg I	eu T	yr	His	Glu	Ala	Asp	Lys	Thr	Tyr	Met	Leu	Arg	Glu	Tyr	Thr	
	.0					15					20					195
tca o	ga g	aa !lii	agc	Larc	att	Ser	agt	Leu	Met	Cat Hie	gtt Val	Dro	Pro	Ser	Leu	193
25	119	, <u></u>	DCI	шуз	30	DCI	DCI		1100	35	val	110	11.0		40	
ttc a	acg g	ſaa	cct	aat	gaa	ata	tcc	cag	tat	tta	cca	ata	aag	gaa	gca	243
Phe 7	thr G	lu	Pro		Glu	Ile	Ser	Gln	_	Leu	Pro	Ile	Lys		Ala	
~++ +	-~+ ~		~	45			995	~	50	- <del>- +</del>	~~+	aat	2 2 C	55	aca	291
gtt t	lys G	lag Hu	Lvs	Leu	Tle	Phe	Pro	Glu	Ara	Ile	Asp	Pro	Asn	Pro	Ala	271
	-,		60					65	5				70			
gac t									taaa	aatgt	tga t	tacaa	acata	at		338
Asp S		ln '5	Lys	Ser	Thr	Gln	Val 80	GIu								
actca			aato	tgac	et ac	acad		a act	atti	ata	agge	artta	att '	tttai	ttatga	398
gaatt																458
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ggg gcg gcc ggc ttc aca cct tcc ctc gat agc gac ttc acc ttt acc Gly Ala Ala Gly Phe Thr Pro Ser Leu Asp Ser Asp Phe Thr Phe Thr 1 5 10 15	148
ctt ccc gcc ggc cag aag gag tgc ttc tac cag ccc atg ccc ctg aag Leu Pro Ala Gly Gln Lys Glu Cys Phe Tyr Gln Pro Met Pro Leu Lys 20 25 30	196
gcc tcg ctg gag atc gag tac caa gtt tta gat gga gca gga tta gat Ala Ser Leu Glu Ile Glu Tyr Gln Val Leu Asp Gly Ala Gly Leu Asp 35 40 45	244
att gat ttc cat ctt gcc tct cca gaa ggc aaa acc tta gtt ttt gaa Ile Asp Phe His Leu Ala Ser Pro Glu Gly Lys Thr Leu Val Phe Glu 50 55 60	292
caa aga aaa tca gat gga gtt cac act gta gag act gaa gtt ggt gat Gln Arg Lys Ser Asp Gly Val His Thr Val Glu Thr Glu Val Gly Asp 65 70 75 80	340
tac atg ttc tgc ttt gac aat aca ttc agc acc att tct gag aag gtg Tyr Met Phe Cys Phe Asp Asn Thr Phe Ser Thr Ile Ser Glu Lys Val 85 90 95	388
att ttc ttt gaa tta atc ctg gat aat atg gga gaa cag gca caa gaa Ile Phe Phe Glu Leu Ile Leu Asp Asn Met Gly Glu Gln Ala Gln Glu 100 105	436
caa gaa gat tgg aag aaa tat att act ggc aca gat ata ttg gat atg Gln Glu Asp Trp Lys Lys Tyr Ile Thr Gly Thr Asp Ile Leu Asp Met 115 120 125	484
aaa ctg gaa gac atc ctg gaa tcc atc agc agc atc aag tcc aga cta Lys Leu Glu Asp Ile Leu Glu Ser Ile Ser Ser Ile Lys Ser Arg Leu 130 135 140	532
agc aaa agt ggg cac ata caa att ctg ctt aga gca ttt gaa gct cgt Ser Lys Ser Gly His Ile Gln Ile Leu Leu Arg Ala Phe Glu Ala Arg 145 150 155 160	580
gat cga aac ata caa gaa agc aac ttt gat aga gtc aat ttc tgg tct Asp Arg Asn Ile Gln Glu Ser Asn Phe Asp Arg Val Asn Phe Trp Ser 165 170 175	628
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atg ctg aag agt ctg ttt gaa gat aag agg aaa agt aga act Met Leu Lys Ser Leu Phe Glu Asp Lys Arg Lys Ser Arg Thr 195 200 205	718
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													gaa Glu			1	00
													gct Ala			1	48
		_		_	-	_					_	_	agg Arg 1	_		1	96
			_	_		_	_	_		-	_		gtg Val		_	2	44
									-		_	_	aat Asn		_	2	92
													gaa Glu			3.	40
													act Thr 65			3	88
													gga Gly			4:	36
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gcc	atg	atc	Thr	cac	gee	acc mb	Tou	Clu	Nan	7 la	T.eu	Ser	Asn	Val	Asp	
	Met	TTe		HIS	val	THE	пеп	-85	Asp	Ата	шси	DCL	-80	• • • •		
			-90				~~~		a = a	a . a	aa.	tac		aaa	cct	96
ctg	ctt	gaa	gag	CTT	ccc	ctc	000	gac	Cag	Cay	Dwa	Crrc	Tla	Clu	Dro	, ,
Leu	Leu		Glu	Leu	Pro	Leu		Asp	GIII	GIII	PLO	-65	116	GIU	FIO	
		-75					-70								ana	144
cca	cct	tcc	tcc	atc	atg	tac	cag	gct	aac	ttt	gac	aca	aac	ווו	gag	7.4.4
Pro	Pro	Ser	Ser	Ile	Met	Tyr	Gln	Ala	Asn	Phe	Asp	Thr	Asn	Phe	GIU	
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Thr	Val	His	Ser	Ser	Met	Asn	Glu	Met	Leu	Glu	Glu	Gly	His	Glu	Tyr	
/	-			-25					-20					-15		
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פרע	1701	Mat	Leu	Tyr	Фhт	Trn	Ara	Ser	Cvs	Ser	Arg	Āla	Ile	Pro	Gln	
Ата	vai	1.16.0	-10	1 y 1	1111	111		-5	-1-		5		1			
			aac	~~~	G 2 G	000	220		at a	aaa	atc	tat	gag	aaq	aca	336
gtg	aaa	tge	Asn	gag	Cay	770	Nan	7×4	Val	Glu	Tle	Tyr	Glu	LVS	Thr	
Val	Lys	Cys	Asn	GIU	GIN		ASII	Arg	vai	Giu	15	1 y 1	OIU	בין כ		
	5					10			~	ata		224	++c	⇒ta	tat	384
gta	gag	gtg	ctg	gag	ccg	gag	gtc	acc	aag	CLC	arg	aay	Dho	Mot	Tare	201
Val	Glu	Val	Leu	Glu		Glu	vai	Thr	Lys		Mec	ьуѕ	Phe	Mec	1 y 1 3 5	
20					25					30						422
ttt	cag	cgc	aag	gcc	atc	gag	cgg	ttc	tgc	agc	gag	gtg	aag	cgg	etg	432
Phe	Gln	Arg	Lys	Ala	Ile	Glu	Arg	Phe	Cys	Ser	Glu	Val	Lys	Arg	Leu	
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tgc	cat	gcc	gag	cgc	agg	aag	gac	ttt	gtc	tct	gag	gcc	tac	ctc	ctg	480
Cys	His	Āla	Glu	Arg	Arg	Lys	Asp	Phe	Val	Ser	Glu	Ala	Tyr	Leu	Leu	
			55					60					65			
acc	ctt	qqc	aag	ttc	atc	aac	atg	ttt	gct	gtc	ctg	gat	gag	cta	aag	528
Thr	Leu	Glv	Lys	Phe	Ile	Asn	Met	Phe	Ala	Val	Leu	Asp	Glu	Leu	Lys	
		70	-1-				75					80				
220	ato	a a m	tgc	agg	atc	aaq	aat.	gac	cac	tcc	qcc	tac	aag	agg	gca	576
) en	Met	Live	Cys	Ser	Val	Lvs	Asn	Asp	His	Ser	Ala	Tyr	Lys	Arg	Ala	
ASII	85	шуы	Cys	DCI		90		1			95	-	•			
~			ctg	-	720		aca	gat	ccc	cag	tet	atc	caq	gag	tca	624
yca 27-	Cay	Dha	Leu	7~~	Tue	Mat	Mla	yen	Dro	Gln	Ser	Tle	Gln	Glu	Ser	
	GIII	Pne	ьeu	Arg		MEC	AIG	rap	110	110	001				115	
100					105		~~~	224	<b>a</b> a <b>c</b>		200	atc	a.c.c	cad		672
cag	aac	ctt	tcc	atg	ELC.	ctg	900	aac	TTi	nac nac	729	T10	Thr	Gln	Cve	• . –
Gln	Asn	Leu	Ser		Phe	Leu	Ala	Asn			Arg	116	1111	130	СуБ	
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ctc	cac	cag	caa	ctt	gaa	gtg	atc	cca	ggc	tat	gag	gag	ctg	clg	710	120
Leu	His	Gln	Gln	Leu	Glu	Val	Ile		GТУ	Tyr	GIu	Glu	ьeu	ьeu	Ala	
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Asp	Ile	Val	Asn	Ile	Cys	Val	Asp	Tyr	Tyr	Glu	Asn	Lys	Met	Tyr	Leu	
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act	ccc	aqt	gag	aaa	cat	atg	ctc	ctc	aag	gta	aaa	ctc	ccc			810
Thr	Pro	Ser	Glu	Lvs	His	Met	Leu	Leu	Lys	Val	Lys	Leu	Pro			
	165		_	<i>1</i> =	_	170			_		175					
tas	ממרר	aca	ccca	taaa	ac c			c cc	tctc	acct	tct	tctt	att	aaaa	atccgt	870
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                       -15
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ggg cta gtg cga agc ccc tcg ctg gac cag atg ttc gac gcc gag
Gly Leu Val Arq Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala Glu
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                                                                   201
ate etg gge tit tee ace eet eea gge egg ete tee atg atg tee tte
Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser Phe
                               20
           15
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ate tte aac gee etc ace tgt gee etg gge ttg etg tae tte ate egg
Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile Arg
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cga gga aag cag tgt ctg gat ttc act gtc act gtc cat ttc ttt cac
Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe His
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                                                                    345
ctc ctg ggc tgc tgg ttc tac agc tcc cgt ttc ccc tcg gcg ctg acc
Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu Thr
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tgg tgg ctg gtc caa gcc gtg tgc att gca ctc atg gct gtc atc ggg
Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile Gly
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gag tac ctg tgc atg cgg acg gag ctc aag gag ata ccc ctc aac tca
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Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn Ser
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gec ect aaa tee aat gte tagaateagg ceetttggae ateeegetga
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Ala Pro Lys Ser Asn Val
    110
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gat gcg gcc caa cag gaa gca aag cac agg gaa gca gaa atg aga aac Asp Ala Ala Gln Gln Glu Ala Lys His Arg Glu Ala Glu Met Arg Asn -25 -20 -15	147
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ctt ata cag atg gca aga tat gga caa cta agt gag aag gta tca gaa Leu Ile Gln Met Ala Arg Tyr Gly Gln Leu Ser Glu Lys Val Ser Glu 20 25 30 35	291
caa ggt tta ata gaa atc ctt aaa aaa gta agc caa caa aca gaa aag Gln Gly Leu Ile Glu Ile Leu Lys Lys Val Ser Gln Gln Thr Glu Lys 40 45 50	339
aca aca aca gtg aaa ttc aac aga aga aaa gta atg gac tct gat gaa Thr Thr Thr Val Lys Phe Asn Arg Arg Lys Val Met Asp Ser Asp Glu  55 60 65	387
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ccg ccg cca ccc ctg tat acc cgg cac cgc atg ctc ggt cca gag tcc Pro Pro Pro Pro Leu Tyr Thr Arg His Arg Met Leu Gly Pro Glu Ser -5 1 5	99
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gca Ala	ctg Leu	ctt Leu	cgc Arg 45	ata	ctg Leu	ccg Pro	gag Glu	tac Tyr 50	cgg Arg	gat Asp	gca Ala	gag Glu	att Ile 55	gtg Val	cgg Arg	24	3
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Ser	75 ttc Phe	aca Thr	gag Glu	acc Thr	atg Met 95	aqc	tcc Ser	ctg Leu	tcc Ser	cct Pro 100	999	agg Arg	ccg Pro	tgg Trp	cag Gln 105	38	.7
90 acc Thr	aag Lys	ctg Leu	agc Ser	Ser	aca	gga Gly	ctc Leu	atc Ile	tat Tyr 115	ctg	cac His	ttc Phe	ggg Gly	cac His 120	aag Lys	43	5
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acc Thr	ctc Leu	tat Tyr 140	125 gac Asp	aag Lys	atg Met	tat Tyr	gag Glu 145	aac	ttt Phe	gtg Val	gag Glu	gag Glu 150	gtg	gat Asp	gct Ala	53	11
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Leu	acc	act Thr	acc Thr	ctg Leu	agt Ser 175	gca	cga Arg	gtt Val	gct Ala	cga Arg 180	ctt	aat Asn	cct Pro	acc Thr	tgg Trp 185	62	37
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Pro	Trp	aag Lys	gag Glu	cat His	ctc Leu 255	tac Tyr	cac His	ctg Leu	gaa Glu	tct Ser 260	Gly ggg	ctg	tac Ser	cct Pro	cca Pro 265	86	67
250 gtg Val	acc	ato	ttc Phe	ttt Phe 270	gtt Val	atc	tac Tyr	act Thr	gac Asp 275	cag Gln	gct	gga Gly	cag Gln	tgg Trp 280	Arg	91	15
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ggt Gly 33(	cac / His	cac	c acc g Thr	cga Arg	gag g Glu 335	ggt Gly	gcc	ttg Leu	ago Ser	atg Met	gcc : Ala	cgt:	gcc Ala	acc Thr	ttg Leu 345	11	07
gco	cag	a Arg	tca y Ser	tac Tyr	cto	cca	caa Glr	ato 1 Ile	tcc Ser	tag		ata	aaac	ctto	ca	11	57

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686

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too cac too agg etg too coo ega aag acc cac tta etg tac atc etc

Ser His Ser Arg Leu Ser Pro Arg Lys Thr His Leu Leu Tyr Ile 160 165 170 agg ccc tct cgg cag ctg taggggtggg gaccggggag cacctgcctg Arg Pro Ser Arg Gln Leu	Leu 175 734									
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Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln Ala Leu Leu  10 20	Arg									
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25 30 35	40									
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Cys Leu Phe Gln Val Pro Glu Ser Ser Leu Ala Phe Gln Thr Asp 60 65 70	_									
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           -30
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       -15
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Asp Phe Leu Arg Ser Leu Ser Asp Gly Asp Ser Gly Thr Ser Glu His
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Arg Leu Leu Pro Pro Pro Ser Leu Leu Ser Leu Glu Ala Pro Ala
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Ser Thr
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Glu Asn Ser Ser Asp Leu Asn Lys Ser Ile Trp Asp Glu Phe Ile Ser  25  30  35  qat qaq qca qat qaa aaq act tat aat gat gca ctt ttt cga tac aat	
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His	Trp	tat Tyr	Ser	Pro	Pro	Glu 75	agg Arg	Thr	Glu	Ser	Pne 80	Asp	vai	gtc Val	1111	342
Lys 85	tgt Cys	Val	Ser	Phe	Thr 90	Leu	Thr	Glu	Gln	Phe 95	.Met	Glu	Lys	ttt Phe	100	390
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His	Trp	tat Tyr	Ser	Pro	Pro	Glu 75	Arg	Thr	GIU	ser	80	Asp	gtg Val	vaı	1111	342
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ccc Pro	Thr	Ile	acc	acg Thr	ggc Gly	Ile	ctc Leu	cat	ctc	ctt Leu	gca Ala 160	Asp	acc Thr	atg Met	ctg Leu	582
gct gcc act	ccca ttaa ctaa	cag lact lcaa ltaa	gaca	igeca :teag iceaa	ac a gag g ict a	tcat actt gctg	cctg ttcc cagc	a go c ac c aa	cat <u>c</u> agct	itgtg :atta	cag gga tct	ctga gcca tact	aca	tcct	agctaa tgtcca tgtgag ataaaa	642 702 762 822 853

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Leu Leu Gly Leu Met Met Val Val Thr Gly Asp Glu Asp Glu Asn Ser	
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ccg tgt gcc cat gag gcc ctc ctg gac gag gac acc ctc ttt tgc cag Pro Cys Ala His Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln	146
10 15 20	
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Gly Leu Glu Val Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val	
25 30 35	
gtt cct gat tgt aac aac tac aga cag aag atc acc tcc tgg atg gag	242
Val Pro Asp Cys Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu 40 45 50	
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Pro Ile Val Lys Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu	
55 60 65 70	
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Val Met Val Asp Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg 75 80 85	
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Phe Trp Arg His Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys	204
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Lys Gly Lys Ile Gln Gly Gln Glu Leu Ser Ala Tyr Gln Ala Pro Ser	
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cca ccg gca cac agt ggc ttc cat cgc tac cag ttc ttt gtc tat ctt Pro Pro Ala His Ser Gly Phe His Arg Tyr Gln Phe Phe Val Tyr Leu	482
120 125 130	
cag gaa gga aag gtc atc tct ctc ctt ccc aag gaa aac aaa act cga	530
Gln Glu Gly Lys Val Ile Ser Leu Leu Pro Lys Glu Asn Lys Thr Arg	
135 140 145 150	
ggc tot tgg aaa atg gac aga ttt otg aac ogt tto cac otg ggc gaa	578
Gly Ser Trp Lys Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu 155 160 165	
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Pro Glu Ala Ser Thr Gln Phe Met Thr Gln Asn Tyr Gln Asp Ser Pro	
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Thr Leu Gln Ala Pro Arg Glu Arg Ala Ser Glu Pro Lys His Lys Asn	
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Leu Pro Asp Glu Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro
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                                    -20
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Arg Leu Leu Tyr Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp
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                                - 5
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Asn Leu Ile Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln
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                                           15
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520

293

301

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gtt Val	aaa Lys 45	aag Lys	att Ile	gca Ala	atg Met	cga Arg 50	gaa Glu	gtc Val	aag Lys	tta Leu	cta Leu 55	aag Lys	caa Gln	ctt Leu	agg Arg	616
cat His 60	gaa Glu	aac Asn	ttg Leu	gtg Val	aat Asn 65	ctc	ttg Leu	gaa Glu	gtg Val	tgt Cys 70	aaa	aaa Lys	aaa Lys	a		659
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gct Ala -10	acc Thr	agc Ser	ctg Leu	gct Ala	ggc Gly -5	cct Pro	gtc Val	ctg Leu	tcc Ser	acc Thr 1	ctc Leu	att Ile	gcc Ala	cca Pro 5	act Thr	103
ccc Pro	atg Met	Leu	ttt Phe 10	tgt Cys	gaa Glu	gat Asp	aaa Lys	agc Ser 15	tgg Trp	gat Asp	ctt Leu	ttt Phe	ctt Leu 20	ttt Phe	ttt Phe	151
aag Lys	tct Ser	cac His 25	aag Lys	aca Thr	tgg Trp	ggc Gly	atc Ile 30	tcc Ser	aca Thr	aat Asn	tta Leu	agt Ser 35	tcc Ser	tgt Cys	cca Pro	199

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Jeu G	ly Phe	e Asn	Lys	Arg	Ala	Ile	Asp	Lys	Cys	Trp	Lys	Ile	Arg	His	
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Asp T	rp Th:	Leu	Ser	Pro	Gly	Glu	His	Ala	Lys	Asp	Glu	Tyr	Val	Leu	
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Tyr T	yr Ty	r Ser	Asn	Leu	Ser	Val	Pro	Ile	Gly	Arg	Phe	Gln	Asn	Arg	
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	is Le														
	0		1		55		- <sub>1</sub> .			60	~~~	u			
	at gt	T CAP	gag	act		cad	aaa	acc	tat		tat	œa a	atc	cac	301
_	sp Va	_		_	_	_					_	_		_	551
65	~_ ~ ~ ~		<u></u>	70			1	~ ***	75	<u>.</u>	~ 1 3			80	
	aa gg	תפת	acc		ata	ttc	aar	220		a+a	a+ a	cta	cat	_	349
	ys Gl														347
u	70 GI	, 014		O 1 1 1		بالدد بد	-y -	_	a	* 44 .4.	· u 1	لما ب ري	95	- 41	
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	61

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Gly	Pro	Cys	Lys		Arg	Asp	Asp	Glu		Val	Cys	Gly	Arg		Leu	
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			gca													505
GIY	ITE	Arg	Ala	GIA	Pro	Asn	Gly		Leu	Phe	Val	Ala		Ala	Cys	
			100					105					110			
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гÀг	GIY		Phe	GIU	vaı	Asn		Trp	Lys	Arg	Glu		ГЛS	Leu	Leu	
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                                    -30
                                                        -25
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            -20
                                -15
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                                                                      208
Ile Val Gly Gly Ser Phe Gly Leu Arg Glu Phe Ser Gln Ile Arg Tyr
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Asp Ala Val Lys Ser Lys Met Asp Pro Glu Leu Glu Lys Lys Leu Lys
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tca ser gcg Ala aca Thr gga Gly gct Ala aaa Lys gtt Val cct Pro atc	agg Arg gng Xaa atc Ile 1 gga Gly aca Thr cta Leu tat Tyr 65 cat His	gtt Val gan Xaa 15g Trp gca Ala act Thr 50 aa Glu caa Gln ttc	atg Met -30 ctg Leu tta Leu atg Met cca Pro 35 ttc Phe tat Tyr gga Gly aat	tca Ser Ctt Leu ttt Phe gtg Val 20 act Thr agt Ser aaa Lys ast	gaa Glu gtc Val aaa Lys 5 tat Tyr gat Asp cca Pro tac Tyr gct Ala 85 tta	aag Lys ttc Phe aat Asn ggc att Ile cca Pro aaa Lys 70 ata Ile ctg	gat Asp aat Asn -10 cat His ctt Leu gaa Glu act Thr 55 aga Arg ctt Leu	gag Glu -25 ttt Phe cga Arg ata Ile agt 40 ctg Leu gaa Glu gaa Glu	tat Tyr ttg Leu ttc Phe atg Met 25 gga Gly ctg Leu ata Ile aag Lys	cag Gln ctc Leu cgc Arg 10 gga Gly act Thr gtt Val agt Ser atg Met 90 ata	ttt Phe atc Ile ttc Phe cta Leu gtc Val aat Asn cag Gln 75 aca Thr	caa Gln ctt Leu -5 ttg Leu att Ile tgt Cys gtc Val 60 cac His ttt Phe cat	cat His -20 acc Thr Cat His tcar gac Asp act Thr aac Asp gca	can Xaa att Ile gaa Glu cga Arg 30 tgt Cys gac Asp atc Ile cca Pro	g Gln 55 nna Xaa ttg Leu act Thr 15 tat Tyr gta Val caa Gln aat Asn gaa Glu 95 tat	105 153 201 249 297 345 393

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145

160

Thr Ala Ala Leu Pro Ala

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165

150 155

175

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          -5
                      1
Ser Pro Val Phe Gln Ile Pro Lys Asn Asp Asp Ile Pro Glu Gln Asp
 10 15
Ser Leu Gly Leu Ser Asn Leu Gln Lys Ser Gln Ile Gln Gly Lys Xaa
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Ala Gly Leu Gln Ser Ser Gly Lys Glu Ala Ala Leu Asn Leu Ser Phe
                45
                                 50
Ile Ser Lys Glu Glu Met Lys Asn Thr Ser Trp Ile Arg Lys Asn Trp
             60
                              65
Leu Leu Val Ala Gly Ile Ser Phe Ile Gly Asp His Leu Gly Thr Tyr
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             ~50
                              -45
Ile Ala Asn Glu Ile Glu Lys Val His Arg Gly Cys Val Ile Ala Asn
          -35
                           -30
                                      -25
Val Val Ser Gly Ser Thr Gly Ile Leu Ser Val Ile Gly Val Met Leu
      -20 -15 -10
Ala Pro Phe Thr Ala Gly Leu Ser Leu Ser Ile Thr Ala Ala Gly Val
       1 5 10
Gly Leu Gly Ile Ala Ser Ala Thr Ala Gly Ile Ala Ser Ser Ile Val
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            15
Glu Asn Thr Tyr Thr Arg Ser Ala Glu Leu Thr Ala Ser Arg Leu Thr
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Ala Thr Ser Thr Asp Gln Leu Glu Ala Leu Arg Asp Ile Leu His Asp
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45 50 55

Ile Thr Pro Asn Val Leu Ser Phe Ala Leu Asp Phe Asp Glu Ala Thr

65 70 Lys Met Ile Ala Asn Asp Val His Thr Leu Arg Arg Ser Lys Ala Thr 80 85 90 Val Gly Arg Pro Leu Ile Ala Trp Arg Tyr Val Pro Ile Asn Val Val 100 105 Glu Thr Leu Arg Thr Arg Gly Ala Pro Thr Arg Ile Val Arg Lys Val 110 115 120 Ala Arg Asn Leu Gly Lys Ala Thr Ser Gly Val Leu Val Val Leu Asp 125 130 135 Val Val Asn Leu Val Gln Asp Ser Leu Asp Leu His Lys Gly Glu Lys 140 145 150 Ser Glu Ser Ala Glu Leu Leu Arg Gln Trp Ala Gln Glu Leu Glu Glu 155 160 165 170 Asn Leu Asn Glu Leu Thr His Ile His Gln Ser Leu Lys Ala Gly 180

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140
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Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val
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Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu
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Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr
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                                         70
Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe
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                                      85
Ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Pro Asp Asn
                        100 105
               95
Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr
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Asp Ser Asp Phe Thr Phe Thr Leu Pro Ala Gly Gln Lys Glu Cys Phe

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Gln Glu
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Arg Arg Gly Arg Ser Gly Ala Gln Val Leu Pro Thr Gly Pro Asp Glu
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Lys Gln Val Glu Lys Ser Glu Val Asp Phe Ser Lys Ser His Ser Leu
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Val Arg Arg Phe Glu Asp Leu Lys Pro Lys Leu Ser Val Cys Lys Thr
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              70
Gly Ser Gln Val Phe Arg Ser Glu Asn Trp Lys Val Trp Ala Glu Ser
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                              90
Ser Arg Gly Asp His Asp Asp Cys Leu Asp Leu Cys Ser Val Leu Cys
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         100
                                  110
Trp Gly Glu Leu Leu Arg Thr Ile Pro Glu Ile Pro Pro Lys Arg Gly
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Gln Val Ser Gln Gln Glu Glu Leu Lys
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Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Leu Glu Ala Leu Ala

-20 -15

- 25

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Val Asp Tyr Ser Ile Gly Arg Asp Ile Gln Arg Gln Asp Leu Ser Ala
        50
Ile Ala Arg Thr Leu Gln Glu Trp Cys Val Gly Cys Glu Val Val Leu
         65
                  70
Ser Gly Ile Glu Glu Gln Val Ser Arg Ala Asn Gln His Lys Glu Gln
          80 85 90
Gln Leu Gly Leu Lys Gln Gln Ile Glu Ser Glu Val Ala Asn Leu Lys
        95 100 105
Lys Thr Ile Lys Val Thr Thr Ala Ala Ala Ala Ala Thr Ser Gln
   110 115 120
Asp Pro Glu Gln His Leu Thr Glu Leu Arg Glu Pro Ala Pro Gly Thr
      130 135
Asn Gln Arg Gln Pro Ser Lys Lys Ala Ser Lys Gly Lys Gly Leu Arg
140 145 150
Gly Ser Ala Lys Ile Trp Ser Lys Ser Asn
```

<210> 159 <211> 24 <212> PRT <213> Homo sapiens

His Ile Asn Ile Ser Phe His Arg

<210> 160 <211> 228 <212> PRT <213> Homo sapiens

<400> 160 Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn Lys 1 5 10 His Ile Asn Ile Ser Phe His Arg Phe Pro Leu Asp Pro Lys Arg Arg Lys Glu Trp Val Arg Leu Val Arg Arg Lys Asn Phe Val Pro Gly Lys His Thr Phe Leu Cys Ser Lys His Phe Glu Ala Ser Cys Phe Asp Leu 55 60 Thr Gly Gln Thr Arg Arg Leu Lys Met Asp Ala Val Pro Thr Ile Phe 75 80 70 Asp Phe Cys Thr His Ile Lys Ser Met Lys Leu Lys Ser Arg Asn Leu 90 95 Leu Lys Lys Asn Asn Ser Cys Ser Pro Ala Gly Pro Ser Ser Leu Lys 105 110 Ser Asn Ile Ser Ser Gln Gln Val Leu Leu Glu His Ser Tyr Ala Phe 125 115 120 Arg Asn Pro Met Glu Ala Lys Lys Arg Ile Ile Lys Leu Glu Lys Glu 130 135 140 Ile Ala Ser Leu Arg Arg Lys Met Lys Thr Cys Leu Gln Lys Glu Arg

```
155
              150
Arg Ala Thr Arg Arg Trp Ile Lys Ala Met Cys Leu Val Lys Asn Leu
     165 170 175
Glu Ala Asn Ser Val Leu Pro Lys Gly Thr Ser Glu His Met Leu Pro
  180 185 190
Thr Ala Leu Ser Ser Leu Pro Leu Glu Asp Phe Lys Ile Leu Glu Gln
195 200 205
Asp Gln Gln Asp Lys Thr Leu Leu Ser Leu Asn Leu Lys Gln Thr Lys
                          220
210 215
Ser Thr Phe Ile
<210> 161
<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 161
Met Asn Leu His Phe Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly
-20 -15 -10 -5
Leu Val Leu Ala Pro Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe
          1 5
Pro Cys Ile Tyr Cys Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala
Phe Ser Phe Ile Thr Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu
30 35
                      40
Ile Leu Pro Glu Lys Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly
                       55
Pro Ala Lys Leu Arg Gln
<210> 162
<211> 44
<212> PRT
<213> Homo sapiens
<400> 162
Met Ser Pro Arg Leu Glu Cys Ser Gly Ala Ile Leu Ala His Cys Asn
                            10
Pro Arg Leu Pro Gly Ser Ser Tyr Ser Pro Ala Ser Ala Thr Trp Val
  20 25
Arg Gly Ser Leu Glu Pro Gly Arg Leu Arg Leu Gln
   35
                      40
<210> 163
<211> 314
<212> PRT
<213> Homo sapiens
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<220>

<221> SIGNAL <222> -58..-1

```
<400> 163
Met Gln Asn Val Ile Asn Thr Val Lys Gly Lys Ala Leu Glu Val Ala
                         -50
Glu Tyr Leu Thr Pro Val Leu Lys Glu Ser Lys Phe Arg Glu Thr Gly
                ~35
Val Ile Thr Pro Glu Glu Phe Val Ala Ala Gly Asp His Leu Val His
                  -20
                                  -15
His Cys Pro Thr Trp Gln Trp Ala Thr Gly Glu Glu Leu Lys Val Lys
              - 5
Ala Tyr Leu Pro Thr Gly Lys Gln Phe Leu Val Thr Lys Asn Val Pro
                        15
Cys Tyr Lys Arg Cys Lys Gln Met Glu Tyr Ser Asp Glu Leu Glu Ala
              30
Ile Ile Glu Glu Asp Asp Gly Asp Gly Gly Trp Val Asp Thr Tyr His
          45
Asn Thr Gly Ile Thr Gly Ile Thr Glu Ala Val Lys Glu Ile Thr Leu
            60
                              65
Glu Asn Lys Asp Asn Ile Arg Leu Gln Asp Cys Ser Ala Leu Cys Glu
      75
                  80
Glu Glu Glu Asp Glu Asp Glu Gly Glu Ala Ala Asp Met Glu Glu Tyr
       90
             95
Glu Glu Ser Gly Leu Leu Glu Thr Asp Glu Ala Thr Leu Asp Thr Arg
            110 115
Lys Ile Val Glu Ala Cys Lys Ala Lys Thr Asp Ala Gly Gly Glu Asp
  120 125 130
Ala Ile Leu Gln Thr Arg Thr Tyr Asp Leu Tyr Ile Thr Tyr Asp Lys
       140 145
Tyr Tyr Gln Thr Pro Arg Leu Trp Leu Phe Gly Tyr Asp Glu Gln Arg
         155 160
Gln Pro Leu Thr Val Glu His Met Tyr Glu Asp Ile Ser Gln Asp His
        170 175 180
Val Lys Lys Thr Val Thr Ile Glu Asn His Pro His Leu Pro Pro
                    190 195
Pro Met Cys Ser Val His Pro Cys Arg His Ala Glu Val Met Lys Lys
 200 205 210
Ile Ile Glu Thr Val Ala Glu Gly Gly Glu Leu Gly Val His Met
215 220 225 230
Tyr Leu Leu Ile Phe Leu Lys Phe Val Gln Ala Val Ile Pro Thr Ile
      235 240
Glu Tyr Asp Tyr Thr Arg His Phe Thr Met
         250
```

<210> 164 <211> 89 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -80..-1 <400> 164 Met Arg Thr Arg Thr Thr Gly Asn Pro Arg Gly Leu His Asp Thr Phe -75 -70 **-**65 Pro Arg Arg Pro Arg Leu Gly Arg Cys Ser Asp Met Asp Thr Ala Arg -60 -55 Thr Ser Cys Ser Asp Leu Leu Pro Trp Glu Gly Val Thr Glu Pro Ala -40 Leu Cys Gly Asp Gln Leu Gln Gly Thr Glu Gly Trp Leu Glu Ala Thr

```
-20
    -30 -25
Gln Leu Gly Arg Gly Leu Leu Ser Ala Cys Ala Pro Trp Gly Asp Gly
-15 -10 -5
Ser Thr Gln Pro Val Pro Leu Cys Ser
1 5
<210> 165
<211> 98
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 165
Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
-15 -10 -5 1
Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu
      5 10 15
Gln Gly Gly Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
            25
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
                               45
 35 40
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Val Phe
50 55 60 65
Arg Arg Glu Leu Ser Glu Tyr Thr Glu Gly Leu Thr Ser Glu Pro Leu
                    75
         70
Thr Ala
<210> 166
<211> 92
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1
<400> 166
Met Leu Val Thr Gln Gly Leu Val Tyr Gln Gly Tyr Leu Ala Ala Asn
 -35 ~30
                                -25
Ser Arg Phe Gly Ser Leu Pro Lys Val Ala Leu Ala Gly Leu Leu Gly
           -15 -10
Phe Gly Leu Gly Lys Val Ser Tyr Ile Gly Val Cys Gln Ser Lys Phe
         1 5
                              10
His Phe Phe Glu Asp Gln Leu Arg Gly Ala Gly Phe Gly Pro Gln His
  15 20
                           25
Asn Arg His Cys Leu Leu Thr Cys Glu Glu Cys Lys Ile Lys His Gly
 30 35 40
```

Leu Ser Glu Lys Gly Asp Ser Gln Pro Ser Ala Ser 45 50 55

<210> 167 <211> 351 <212> PRT

```
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 167
Met Val Pro Phe Ile Tyr Leu Gln Ala His Phe Thr Leu Cys Ser Gly
 -15 -10 -5
Trp Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val Tyr Val Pro Tyr
1 5
               10
Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu Val Ser Ile
 20
Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala Ala Ile Thr
Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu Gly Ile Leu
Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp Ser Pro Glu Pro
65 70
                   75
Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro Asn Leu Phe Ser
                90
Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser Glu Val Leu
        100 105
Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile Asp His Ser Leu
     115 120
                                    125
Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu Trp Tyr Tyr
  130 135 140
Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln Asp Leu Lys Met
   150 155 160
Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp Ser Gly Thr
          165 170 175
Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala Val Lys Ser
         180 185 190
Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp Gly Phe Trp Leu
      195 200 205
Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr Pro Trp Asn Ile
  210 215
                                 220
Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val Thr Asn Gln Ser
225 230
                             235 240
Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro Val Glu Asp
            245 250 255
Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile Ser Gln Ser
        260
                        265 270
Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly Phe Tyr Val
                     280 285
Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val Ser Ala Cys
                  295
His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly Pro Phe Cys
              310
                              315
His Leu Gly His Gly Arg Leu Trp Leu Gln His Ser Thr Asp Arg
            325
                        330
```

```
<210> 168
<211> 138
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -47..-1
```

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```
<400> 168
Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu
  -45 -40 -35
Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro Phe Val Ser
                   -25
Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys Ala Cys Ile
-15 -10
                        -5
Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu
                        10
Ala Gly Leu Cys Thr Leu Gly Ser Val Ser Cys Tyr Val Ala Gly Ile
                       25
Glu Leu Leu His Gln Lys Leu Glu Leu Pro Asp Asn Val Ser Gly Glu
                   40
Phe Gly Trp Ser Phe Cys Leu Ala Cys Val Ser Ala Pro Leu Gln Phe
                     60
               55
Met Ala Ser Ala Leu Phe Ile Trp Ala Ala His Thr Asn Arg Arg Glu
                  75
Tyr Thr Leu Met Lys Ala Tyr Arg Val Ala
```

```
<210> 169
<211> 101
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -73..-1
<400> 169
Met Asn Leu Glu Arg Val Ser Asn Glu Glu Lys Leu Asn Leu Cys Arg
                 ~65
Lys Tyr Tyr Leu Gly Gly Phe Ala Phe Leu Pro Phe Leu Trp Leu Val
                    -50
    -55
Asn Ile Phe Trp Phe Tyr Arg Glu Ala Phe Leu Val Pro Ala Tyr Thr
                  -35 -30
Glu Gln Ser Gln Ile Lys Gly Tyr Val Trp Arg Ser Ala Val Gly Phe
                              -15 -10
                -20
Leu Phe Trp Val Ile Val Leu Thr Ser Trp Ile Thr Ile Phe Gln Ile
                       1 5
           -5
Tyr Arg Pro Arg Trp Gly Ala Leu Gly Asp Tyr Leu Ser Phe Thr Ile
                  15
 10
Pro Leu Gly Thr Pro
  25
```

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```
Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val
                        -45
Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser
                            -25
              -30
Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro
                        -10
                -15
Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly
                  5
       1
Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His
              20
Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu
             35
                                     40
Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys
                50
                                  55
Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe
             65
                              70
Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro
                           85
Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn
                       100
                               105
Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu
                           120
          115
Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro
                130
                        135
Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Ser Asp
                              150
            145
Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly
                           165
         160
Glu Ala Lys Asp Gly Ser Asn Leu Cys Phe Ser Lys
```

<210> 171 <211> 350 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -68..-1

<400> 171 Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -60 -55 - 65 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -30 -25 Ala Ser Ala Arq Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -10 -15 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 3.5 40 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 55 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe Arg Leu Lys Ile Pro Pro Phe Glu Lys Ala Arg Ser Val Leu Glu Ala

WO 99/31236 -129- PCT/IB98/02122 -

```
8.5
                                      90
        8.0
Leu Gln Gln His Arg Pro Ser Pro Glu Leu Thr Leu Ser Gln Lys Ile
            100
Arg Thr Lys Leu Gln Asn Pro Asp Leu Leu Glu Leu Cys His Ser Val
                        120
        115
Pro Lys Glu Val Asp Gln Leu Gly Gly Arg Gly Tyr Gly Ser Glu Ser
                     135
             130
Gly Glu Glu Asp Phe Ala Ala Phe Arg Ala Trp Leu Arg Cys Tyr Gly
           145 150 155
Met Pro Gly Met Ser Ser Leu Gln Asp Arg His Gly Arg Thr Ile Trp
        160 165 170
Phe Gln Gly Asp Pro Gly Pro Leu Ala Pro Lys Gly Arg Lys Ser Arg
                          185
    175 180
Lys Lys Lys Ser Lys Ala Thr Gln Leu Ser Pro Glu Asp Arg Val Glu
        195 200
Asp Ala Leu Pro Pro Ser Lys Ala Pro Ser Lys Thr Arg Arg Ala Lys
205 210 215
Arg Asp Leu Pro Lys Arg Thr Ala Thr Gln Arg Pro Glu Gly Thr Ser
         225 230 235
Leu Gln Gln Asp Pro Glu Ala Pro Thr Val Pro Lys Lys Gly Arg Arg
      240 245 250
Lys Gly Arg Gln Ala Ala Ser Gly His Cys Arg Pro Arg Lys Val Lys
   255 260
Ala Asp Ile Pro Ser Leu Glu Pro Glu Gly Thr Ser Ala Ser
                 275
```

<211> 390 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -68..-1 <400> 172 Met Pro Glu Gly Pro Glu Leu His Leu Ala Ser Gln Phe Val Asn Glu -65 -60 -55 Ala Cys Arg Ala Leu Val Phe Gly Gly Cys Val Glu Lys Ser Ser Val -45 Ser Arg Asn Pro Glu Val Pro Phe Glu Ser Ser Ala Tyr Arg Ile Ser -35 -30 -25 Ala Ser Ala Arg Gly Lys Glu Leu Arg Leu Ile Leu Ser Pro Leu Pro -15 -10 -5 Gly Ala Gln Pro Gln Gln Glu Pro Leu Ala Leu Val Phe Arg Phe Gly Met Ser Gly Ser Phe Gln Leu Val Pro Arg Glu Glu Leu Pro Arg His 20 Ala His Leu Arg Phe Tyr Thr Ala Pro Pro Gly Pro Arg Leu Ala Leu 35 Cys Phe Val Asp Ile Arg Arg Phe Gly Arg Trp Asp Leu Gly Gly Lys 50 Trp Gln Pro Gly Arg Gly Pro Cys Val Leu Gln Glu Tyr Gln Gln Phe 65 Arg Glu Asn Val Leu Arg Asn Leu Ala Asp Lys Ala Phe Asp Arg Pro Ile Cys Glu Ala Leu Leu Asp Gln Arg Phe Phe Asn Gly Ile Gly Asn 95 100 105 Tyr Leu Arg Ala Glu Ile Leu Tyr Arg Leu Lys Ile Pro Pro Phe Glu

115

<210> 172

WO 99/31236 -130- PCT/IB98/02122 .

```
Lys Ala Arg Ser Val Leu Glu Ala Leu Gln Gln His Arg Pro Ser Pro
             130
                           135
Glu Leu Thr Leu Ser Gln Lys Ile Arg Thr Lys Leu Gln Asn Pro Asp
               150
          145
Leu Leu Glu Leu Cys His Ser Val Pro Lys Glu Val Val Gln Leu Gly
                          170
       160 165
Gly Arg Gly Tyr Gly Ser Glu Ser Gly Glu Glu Asp Phe Ala Ala Phe
                         185
    175
           180
Arg Ala Trp Leu Arg Cys Tyr Gly Met Pro Gly Met Ser Ser Leu Gln
        195 200
Asp Arg His Gly Arg Thr Ile Trp Phe Gln Gly Asp Pro Gly Pro Leu
    210 215 220
Ala Pro Lys Gly Arg Lys Ser Arg Lys Lys Lys Ser Lys Ala Thr Gln
          225 230 235
Leu Ser Pro Glu Asp Arg Val Glu Asp Ala Leu Pro Pro Ser Lys Ala
 240 245 250
Pro Ser Arg Thr Arg Arg Ala Lys Arg Asp Leu Pro Lys Arg Thr Ala
255 260 265
Thr Gln Arg Pro Glu Gly Thr Ser Leu Gln Gln Asp Pro Glu Ala Pro
 270 275 280
Thr Val Pro Lys Lys Gly Arg Arg Lys Gly Arg Gln Ala Ala Ser Gly
285 290 295 300
His Cys Arg Pro Arg Lys Val Lys Ala Asp Ile Pro Ser Leu Glu Pro
        305
                  310
Glu Gly Thr Ser Ala Ser
       320
```

<210> 173 <211> 190 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -82..-1 <400> 173 Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe -80 -75 -70 His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly -65 -60 Val Ser Leu Pro Gly Ile Leu Thr Ala Lys Cys Gly Ala Glu Val Ile -50 ~45 -40 Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln -30 -25 Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr -15 -10 -5 Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile 10 5 Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Asp Phe Glu Asp Ile 20 25 Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu 40 3.5 Trp Ser Thr Tyr Gln Val Arg Ser Ala Asp Trp Ser Leu Glu Ala Leu 5.0 55 Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser Phe 65 70 Asp Ala Asp Lys Glu Asp Ile Ala Glu Ser Thr Leu Pro Gly Arg His 85 Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu

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95 100 105

<210> 174 <211> 285 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -232..-1 <400> 174 Met Gly Cys Val Phe Gln Ser Thr Glu Asp Lys Arg Ile Phe Lys Ile -230 -225 -220 Asp Trp Thr Leu Ser Pro Gly Glu His Ala Lys Asp Glu Tyr Val Leu -215 -210 -205 Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg -200 -195 -190 -185 Val His Leu Met Gly Asp Asn Leu Cys Asn Asp Gly Ser Leu Leu Leu -180 -175 Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg -165 -160 -155 Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val -150 **-**145 -140 Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile -135 -130 -125 Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys -110 -120 -115 Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Glu Glu Ile Val Phe **-100 -95 -90** Arg Tyr Tyr His Lys Leu Arg Met Ser Ala Glu Tyr Ser Gln Ser Trp -85 -80 Gly His Phe Gln Asn Arg Val Asn Leu Val Gly Asp Ile Phe Arg Asn -70 -65 Asp Gly Ser Ile Met Leu Gln Gly Val Arg Glu Ser Asp Gly Gly Asn ~55 -50 -45 Tyr Thr Cys Ser Ile His Leu Gly Asn Leu Val Phe Lys Lys Thr Ile -40 -35 -30 Val Leu His Val Ser Pro Glu Glu Pro Arg Thr Leu Val Thr Pro Ala -20 -15 -10 Ala Leu Arg Pro Leu Val Leu Gly Gly Asn Gln Leu Val Ile Ile Val -5 1 5 Gly Ile Val Cys Ala Thr Ile Leu Leu Leu Pro Val Leu Ile Leu Ile 15 20 Val Lys Lys Thr Cys Gly Asn Lys Ser Ser Val Asn Ser Thr Val Leu 30 35 Val Lys Asn Thr Lys Lys Thr Asn Pro Lys Lys Lys 45

<210> 175 <211> 153 <212> PRT <213> Homo sapiens

```
25
Tyr Tyr Tyr Ser Asn Leu Ser Val Pro Ile Gly Arg Phe Gln Asn Arg
 35 40
Val His Leu Met Gly Asp Ile Leu Cys Asn Asp Gly Ser Leu Leu
Gln Asp Val Gln Glu Ala Asp Gln Gly Thr Tyr Ile Cys Glu Ile Arg
                          . 75
Leu Lys Gly Glu Ser Gln Val Phe Lys Lys Ala Val Val Leu His Val
                               90
Leu Pro Glu Glu Pro Lys Glu Leu Met Val His Val Gly Gly Leu Ile
   100 105
Gln Met Gly Cys Val Phe Gln Ser Thr Glu Val Lys His Val Thr Lys
            120
Val Glu Trp Ile Phe Ser Gly Arg Arg Ala Lys Val Thr Arg Arg Lys
                  135
His His Cys Val Arg Glu Gly Ser Gly
                  150
<210> 176
<211> 49
<212> PRT
<213> Homo sapiens
<400> 176
Met Leu Xaa Gly Asp His Arg Ala Leu Leu Leu Lys Ile Trp Leu Leu
Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val
       20
                             25
Met Glu Arg Arg Val Lys Met Thr Ser Cys Pro Ser Cys Pro Arg Phe
Cys
<210> 177
<211> 99
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 177
Met Lys Ser Ala Lys Leu Gly Phe Leu Leu Arg Phe Phe Ile Phe Cys
              -20
                                 -15
Ser Leu Asn Thr Leu Leu Leu Gly Gly Val Asn Lys Ile Ala Glu Lys
                             1
Ile Cys Gly Asp Leu Lys Asp Pro Cys Lys Leu Asp Met Asn Phe Gly
                      15
Ser Cys Tyr Glu Val His Phe Arg Tyr Phe Tyr Asn Arg Thr Ser Lys
                                  35
                  3.0
Arg Cys Glu Thr Phe Val Phe Ser Gly Cys Asn Gly Asn Leu Asn Asn
                                50
Phe Lys Leu Lys Ile Glu Arg Glu Val Ala Cys Val Ala Lys Tyr Lys
Pro Pro Arg
```

75

```
<210> 178
<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 178
Met Ala Ser Pro Ala Val Asn Arg Trp Lys Arg Pro Arg Leu Lys Pro
    -35
                         -30
Val Trp Pro Arg Arg Leu Glu Ser Trp Leu Leu Leu Asp Ala Leu Leu
                                 -10
                     ~15
Arg Leu Gly Asp Thr Lys Lys Lys Arg Gln Pro Glu Ala Ala Thr Lys
Ser Cys Val Arg Ser Ser Cys Gly Gly Pro Ser Gly Asp Gly Pro Pro
        15
                         20
Pro Cys Leu Gln Gln Pro Asp Pro Arg Ala Leu Ser Gln Ala Phe Ser
               35
Arg Ser Phe Pro Leu Phe Pro Ser Leu Ala Gly Lys Ser Met Ile
               50
<210> 179
<211> 121
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 179
Met Met Leu Pro Gln Trp Leu Leu Leu Phe Leu Leu Phe Phe Phe
    -20 -15 -10
Leu Phe Leu Leu Thr Arg Gly Ser Leu Ser Pro Thr Lys Tyr Asn Leu
                       1
Leu Glu Leu Lys Glu Ser Cys Ile Arg Asn Gln Asp Cys Glu Thr Gly
                                    20
                 15
Cys Cys Gln Arg Ala Pro Asp Asn Cys Glu Ser His Cys Ala Glu Lys
              30
                                3.5
Gly Ser Glu Gly Ser Leu Cys Gln Thr Gln Val Phe Phe Gly Gln Tyr
                            50
          45
Arg Ala Cys Pro Cys Leu Arg Asn Leu Thr Cys Ile Tyr Ser Lys Asn
                         65
Glu Lys Trp Leu Ser Ile Ala Tyr Gly Arg Cys Gln Lys Ile Gly Arg
                     80
Gln Lys Leu Ala Lys Lys Met Phe Phe
<210> 180
<211> 59
```

<213> Homo sapiens
<400> 180
Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg

<212> PRT

<210> 181 <211> 86 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -14..-1

<400> 181 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -10 - 5 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Pro Arg Ser Ser Ala 10 15 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 25 30 Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 40 45 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly 55 60

Tyr Arg Ile Cys Asp Leu 70

<210> 182 <211> 165 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1

<400> 182 Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -50 -55 -45 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro ~35 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -20 -15 Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val -10 -5 1 Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Val Ser Phe Leu 15 Thr Phe Asp Leu Leu His Arg Pro Ala Gly His Thr Leu Pro Gln Arg 30 Lys Leu Leu Thr Arg Gly Gln Ser Gln Gly Ala Gly Glu Gly Pro Gly 45 50 Gln Gln Glu Ala Leu Leu Gln Met Gly Thr Val Ser Gly Gln Leu 60 65 Ser Leu Gln Asp Ala Leu Leu Leu Leu Met Gly Leu Gly Pro Leu

```
80
 Leu Arg Ala Cys Gly Met Pro Leu Thr Leu Leu Gly Leu Ala Phe Cys
                  95
     90
 Leu His Pro Trp Ala
      105
 <210> 183
 <211> 80
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SIGNAL
 <222> -35..-1
 <400> 183
 Met Pro Phe Gln Phe Gly Thr Gln Pro Arg Arg Phe Pro Val Glu Gly
 -35 -30 -25 -20
. Gly Asp Ser Ser Ile Glu Leu Glu Pro Gly Leu Ser Ser Ser Ala Ala
                               -10
              -15
 Cys Asn Gly Lys Glu Met Ser Pro Thr Arg Gln Leu Arg Arg Cys Pro
  Gly Ser His Cys Leu Thr Ile Thr Asp Val Pro Val Thr Val Tyr Ala
    15 20
  Thr Thr Arg Lys Pro Pro Ala Gln Ser Ser Lys Glu Met His Pro Lys
    35 40 45
  <210> 184
  <211> 73
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -21..-1
  Met Ala Pro Gln Thr Leu Leu Pro Val Leu Val Leu Cys Val Leu Leu
                   -15 -10
  Leu Gln Ala Gln Gly Gly Tyr Arg Asp Lys Met Arg Met Gln Arg Ile
                               5
                  1
  Lys Val Cys Glu Lys Arg Pro Ser Ile Asp Leu Cys Ile His His Cys
                20
           15
  Ser Cys Phe Gln Lys Cys Glu Thr Asn Lys Ile Cys Cys Ser Ala Phe
                      35
       30
  Cys Gly Asn Ile Cys Met Ser Ile Leu
    45
  <210> 185
  <211> 98
  <212> PRT
  <213> Homo sapiens
  <400> 185
  Met Leu Gly Ala Glu Thr Glu Glu Lys Leu Phe Asp Ala Pro Leu Ser
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10

 Ile
 Ser
 Lys
 Arg
 Glu
 Gln
 Leu
 Glu
 Gln
 Gln
 Gln
 Gln
 Val
 Pro
 Glu
 Asn
 Tyr
 Phe

 Tyr
 Val
 Pro
 Asp
 Leu
 Gly
 Gln
 Val
 Pro
 Glu
 Ile
 Asp
 Val
 Pro
 Ser
 Tyr

 Leu
 Pro
 Asp
 Leu
 Pro
 Gly
 Ile
 Ala
 Asp
 Leu
 Met
 Tyr
 Ile
 Ala
 Asp

 Leu
 Gly
 Pro
 Gly
 Ile
 Ala
 Pro
 Ser
 Ala
 Pro
 Gly
 Thr
 Ile
 Ala
 Asp

 65
 70
 75
 75
 Thr
 Tyr
 Lys
 Met

 67
 70
 80
 90
 90
 95
 Met

 80
 90
 95
 95
 95

<210> 186 <211> 112 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 186 Met Glu Ser Arg Val Leu Leu Arg Thr Phe Cys Leu Ile Phe Gly Leu ~15 -10 Gly Ala Val Trp Gly Leu Gly Val Asp Pro Ser Leu Gln Ile Asp Val 1 5 Leu Thr Glu Leu Glu Leu Gly Glu Ser Thr Thr Gly Val Arg Gln Val 15 20 Pro Gly Leu His Asn Gly Thr Lys Ala Phe Leu Phe Gln Asp Thr Pro 35 4 0 Arg Ser Ile Lys Ala Ser Thr Ala Thr Ala Glu Gln Phe Phe Gln Lys 55 Leu Arg Asn Lys His Glu Phe Thr Ile Leu Val Thr Leu Lys Gln Thr 70 His Leu Asn Ser Gly Val Ile Leu Ser Ile His His Leu Asp His Arg 80

<210> 187 <211> 70 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -44..-1

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<211> 92
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 188
Met Leu Phe Ser Leu Ser Leu Ser Asn Leu Asn Gln Ile Gly Ser
              <del>-</del> 5
Ser His Leu Asp Arg Pro His Ile Pro Gly Gln Ser Ala Gln Leu Phe
                  10
                                     15
Ile Tyr Gln Met Ser Ser Gln Gln Leu Gln Gln Gln Pro Ser Ala Asn
                      30
       25
Lys Lys Ala Gly Lys Ile His Asn Thr Pro Phe Ala Asn Gln Leu Asn
             40 45
Pro Thr Gln His Leu Ala Lys Pro Phe Gln Gln Ile Leu Pro Gly Arg
               60
Gln Ser Gly Ser Leu Thr Ser Pro Phe Leu Ala Cys
                75
<210> 189
<211> 207
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
 <400> 189
Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala
                                          -30
                         -35
 Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe
                                     -15
                      -20
 Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Pro Ile Ile
                                 1
 -10 -5
 Leu Gln Glu Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser
                            15
 Ala Ile Tyr Ala Ser Gln Thr Glu Gln Glu Tyr Leu Lys Ile Glu Lys
                                          35
           30
 Val Asp Leu Pro Leu Ile Asp Ser Leu Ile Arg Val Leu Gln Asn Met
                                       50
                     45
 Glu Gln Cys Gln Lys Lys Pro Glu Asn Ser Ala Glu Ser Asn Thr Glu
                          65 . 70
         60
 Glu Thr Lys Arg Thr Asp Leu Thr Gln Asp Asp Leu His Leu Lys Ile
                               80
               75
 Leu Lys Asp Ile Leu Cys Glu Phe Leu Ser Asn Ile Phe Gln Ala Leu
                             95
 Thr Lys Glu Thr Val Ala Gln Gly Val Lys Glu Gly Gln Leu Ser Lys
```

110 Gln Lys Cys Ser Ser Ala Phe Gln Asn Leu Leu Pro Phe Tyr Ser Pro

Val Val Glu Asp Phe Ile Lys Ile Leu Arg Glu Val Asp Lys Ala Leu 135 140 145 150 Alæ Asp Asp Leu Glu Lys Asn Phe Pro Ser Leu Lys Val Gln Thr

120 125

115

155

160

165

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<210> 190
<211> 201
<212> PRT
<213> Homo sapiens
<400> 190
Met Gln Val Ala Leu Lys Glu Asp Leu Asp Ala Leu Lys Glu Lys Phe
                            10
Arg Thr Met Glu Ser Asn Gln Lys Ser Ser Phe Gln Glu Ile Pro Lys
   20
                          25
Leu Asn Glu Glu Leu Leu Ser Lys Gln Lys Gln Leu Glu Lys Ile Glu
                      40
Ser Gly Glu Met Gly Leu Asn Lys Val Trp Ile Asn Ile Thr Glu Met
                55
                                60
Asn Lys Gln Ile Ser Leu Leu Thr Ser Ala Val Asn His Leu Lys Ala
      70
                             75 80
Asn Val Lys Ser Ala Ala Asp Leu Ile Ser Leu Pro Thr Thr Val Glu
                            90 95
            85
Gly Leu Gln Lys Ser Val Ala Ser Ile Gly Asn Thr Leu Asn Ser Val
         100 105 110
His Leu Ala Val Glu Ala Leu Gln Lys Thr Val Asp Glu His Lys Lys
                     120
                                     125
Thr Met Glu Leu Leu Gln Ser Asp Met Asn Gln His Phe Leu Lys Glu
                   135 140
Thr Pro Gly Ser Asn Gln Ile Ile Pro Ser Pro Ser Ala Thr Ser Glu
145 150
                               155 160
Leu Asp Asn Lys Thr His Ser Glu Asn Leu Lys Gln Met Gly Asp Arg
            165 170
Ser Ala Thr Leu Lys Arg Gln Ser Leu Asp Gln Val Thr Asn Arg Thr
        180
Asp Thr Val Lys Ile Gln Lys Lys
                     200
```

<210> 191

<211> 379

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -37..-1

<400> 191

Met Pro His Ser Ser Leu His Pro Ser Ile Pro Cys Pro Arg Gly His
-35
-30
-25

Gly Ala Gln Lys Ala Ala Leu Val Leu Ser Ala Cys Leu Val Thr
-20 -15 -10

Leu Trp Gly Leu Gly Glu Pro Pro Glu His Thr Leu Arg Tyr Leu Val
-5 1 5 10

Leu His Leu Ala Ser Leu Gln Leu Gly Leu Leu Leu Asn Gly Val Cys
20
25

Ser Leu Ala Glu Glu Leu Arg His Ile His Ser Arg Tyr Arg Gly Ser 30 35 40

Tyr Trp Arg Thr Val Arg Ala Cys Leu Gly Cys Pro Leu Arg Arg Gly
45 50 55

Ala Leu Leu Leu Ser Ile Tyr Phe Tyr Tyr Ser Leu Pro Asn Ala

```
70
               65
Val Gly Pro Pro Phe Thr Trp Met Leu Ala Leu Leu Gly Leu Ser Gln
                           85
Ala Leu Asn Ile Leu Leu Gly Leu Lys Gly Leu Ala Pro Ala Glu Ile
                        100
Ser Ala Val Cys Glu Lys Gly Asn Phe Asn Val Ala His Gly Leu Ala
                            120
                     115
Trp Ser Tyr Tyr Ile Gly Tyr Leu Arg Leu Ile Leu Pro Glu Leu Gln
                  130
Ala Arg Ile Arg Thr Tyr Asn Gln His Tyr Asn Asn Leu Leu Arg Gly
             145 150
Ala Val Ser Gln Arg Leu Tyr Ile Leu Leu Pro Leu Asp Cys Gly Val
           160 165 170
Pro Asp Asn Leu Ser Met Ala Asp Pro Asn Ile Arg Phe Leu Asp Lys
        175 180
Leu Pro Gln Gln Thr Gly Asp Arg Ala Gly Ile Lys Asp Arg Val Tyr
                     195
Ser Asn Ser Ile Tyr Glu Leu Leu Glu Asn Gly Gln Arg Ala Gly Thr
                  210 215
Cys Val Leu Glu Tyr Ala Thr Pro Leu Gln Thr Leu Phe Ala Met Ser
                      230 235
              225
Gln Tyr Ser Gln Ala Gly Phe Ser Arg Glu Asp Arg Leu Glu Gln Ala
                          245 250
           240
Lys Leu Phe Cys Arg Thr Leu Glu Asp Ile Leu Ala Asp Ala Pro Glu
                        260 265
       255
Ser Gln Asn Asn Cys Arg Leu Ile Ala Tyr Gln Glu Pro Ala Asp Asp
                     275 280
Ser Ser Phe Ser Leu Ser Gln Glu Val Leu Arg His Leu Arg Gln Glu
       290 295
Glu Lys Glu Glu Val Thr Val Gly Ser Leu Lys Thr Ser Ala Val Pro
    305 310
Ser Thr Ser Thr Met Ser Gln Glu Pro Glu Leu Leu Ser Gly Met
          320 325
Gly Lys Pro Leu Pro Leu Arg Thr Asp Phe Ser
        335
```

<210> 192 <211> 112 <212> PRT <213> Homo sapiens

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<211> 43
<212> PRT
<213> Homo sapiens
<400> 193
Ser Leu Pro Gln Ala Leu Trp Phe Gln Phe Phe Tyr His Ser Gly Ser
                    10 15
Ser Leu Glu Ser Pro Gly Met Leu Asn Gly Pro Phe Gln His Arg Asn
          20
                             25
Ser Arg Ile Met Thr His Arg Ser Ala Glu Lys
<210> 194
<211> 51
<212> PRT
<213 > Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 194
Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser Met Leu Ser Arg Ala
           -10
                                       - 5
Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln Gln Phe Ser Tyr Leu
                               10
Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly Asn Val Leu Gln Leu
          20
Pro Asn Phe
 3.5
<210> 195
<211> 244
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 195
Met Ala Asn Pro Lys Leu Leu Gly Leu Glu Leu Ser Glu Ala Glu Ala
          -15 -10 -5
Ile Gly Ala Asp Ser Ala Arg Phe Glu Glu Leu Leu Gln Ala Ser
                                      10
Lys Glu Leu Gln Gln Ala Gln Thr Thr Arg Pro Glu Ser Thr Gln Ile
15
      20
                                  25
Gln Pro Gln Pro Gly Phe Cys Ile Lys Thr Asn Ser Ser Glu Gly Lys
            35
                               40
Val Phe Ile Asn Ile Cys His Ser Pro Ser Ile Pro Pro Pro Ala Asp
               55
         50
Val Thr Glu Glu Glu Leu Gln Met Leu Glu Glu Asp Gln Ala Gly
          70
                                          75
Phe Arg Ile Pro Met Ser Leu Gly Glu Pro His Ala Glu Leu Asp Ala
                  85
                                   90
Lys Gly Gln Gly Cys Thr Ala Tyr Asp Val Ala Val Asn Ser Asp Phe
                 100
```

Tyr Arg Arg Met Gln Asn Ser Asp Phe Leu Arg Glu Leu Val Ile Thr

```
125
           115
Ile Ala Arg Glu Gly Leu Glu Asp Ile Tyr Asn Leu Gln Leu Asn Pro
              135
        130
Glu Trp Arg Met Met Lys Asn Arg Pro Phe Met Gly Ser Ile Ser Gln
           150 155
Gln Asn Ile Arg Ser Glu Gln Arg Pro Arg Ile Gln Glu Leu Gly Asp
      165 170
Leu Tyr Thr Pro Ala Pro Gly Arg Ala Glu Ser Gly Pro Glu Lys Pro
                    185 190
175 180
His Leu Asn Leu Trp Leu Glu Ala Pro Asp Leu Leu Ala Glu Val
      195 200 205
Asp Leu Pro Lys Leu Asp Gly Ala Leu Gly Leu Ser Leu Glu Ile Gly
      210 215
Arg Thr Ala Trp
    225
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<210> 196 <211> 353 <212> PRT <213> Homo sapiens

<222> -34..-1

<221> SIGNAL

<400> 196 Met Glu Arg Gly Leu Lys Ser Ala Asp Pro Arg Asp Gly Thr Gly Tyr -30 -25 -20 Thr Gly Trp Ala Gly Ile Ala Val Leu Tyr Leu His Leu Tyr Asp Val -10 --5 -15 Phe Gly Asp Pro Ala Tyr Leu Gln Leu Ala His Gly Tyr Val Lys Gln Ser Leu Asn Cys Leu Thr Lys Arg Ser Ile Thr Phe Leu Cys Gly Asp 25 20 Ala Gly Pro Leu Ala Val Ala Ala Val Leu Tyr His Lys Met Asn Asn 35 Glu Lys Gln Ala Glu Asp Cys Ile Thr Arg Leu Ile His Leu Asn Lys 55 Ile Asp Pro His Ala Pro Asn Glu Met Leu Tyr Gly Arg Ile Gly Tyr 70 . Ile Tyr Ala Leu Leu Phe Val Asn Lys Asn Phe Gly Val Glu Lys Thr 85 90 Pro Gln Ser His Ile Gln Gln Ile Cys Glu Thr Ile Leu Thr Ser Gly 100 105 110 Glu Asn Leu Ala Arg Lys Arg Asn Phe Thr Ala Lys Ser Pro Leu Met 120 125 115 Tyr Glu Trp Tyr Gln Glu Tyr Tyr Val Gly Ala Ala His Gly Leu Ala 135 140 130 Gly Ile Tyr Tyr Tyr Leu Met Gln Pro Ser Leu Gln Val Ser Gln Gly 150 155 Lys Leu His Ser Leu Val Lys Pro Ser Val Asp Tyr Val Cys Gln Leu 165 170 Lys Phe Pro Ser Gly Asn Tyr Pro Pro Cys Ile Gly Asp Asn Arg Asp 180 185 190 Leu Leu Val His Trp Cys His Gly Ala Pro Gly Val Ile Tyr Met Leu 195 200 205 Ile Gln Ala Tyr Lys Val Phe Arg Glu Glu Lys Tyr Leu Cys Asp Ala 210 215 220

Tyr Gln Cys Ala Asp Val Ile Trp Gln Tyr Gly Leu Leu Lys Lys Gly
225 230 235

WO 99/31236 -142-PCT/IB98/02122

Tyr Gly Leu Cys His Gly Ser Ala Gly Asn Ala Tyr Ala Phe Leu Thr 245 250 Leu Tyr Asn Leu Thr Gln Asp Met Lys Tyr Leu Tyr Arg Ala Cys Lys 260 265 Phe Ala Glu Trp Cys Leu Glu Tyr Gly Glu His Gly Cys Arg Thr Pro 275 280 Asp Thr Pro Phe Ser Leu Phe Glu Gly Met Ala Gly Thr Ile Tyr Phe 290 295 Leu Ala Asp Leu Leu Val Pro Thr Lys Ala Arg Phe Pro Ala Phe Glu 310

<210> 197 <211> 30 <212> PRT <213> Homo sapiens

<400> 197 Met Gln Met Asp Thr Phe Phe Met Ser Glu Lys His Thr His Thr His 1 5 10 Thr His Ile His Thr His Thr Arg Lys Thr Lys Lys Lys 20 25

<210> 198 <211> 112 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -48..-1

<400> 198 Met Gln Asp Thr Gly Ser Val Val Pro Leu His Trp Phe Gly Phe Gly -45 -40 -35 Tyr Ala Ala Leu Val Ala Ser Gly Gly Ile Ile Gly Tyr Val Lys Ala -30 -25 -20 Gly Ser Val Pro Ser Leu Ala Ala Gly Leu Leu Phe Gly Ser Leu Ala -15 -10 -5 Gly Leu Gly Ala Tyr Gln Leu Ser Gln Asp Pro Arg Asn Val Trp Val 1 5 10 15

Phe Leu Ala Thr Ser Gly Thr Leu Ala Gly Ile Met Gly Met Arg Phe 25 20 Tyr His Ser Gly Lys Phe Met Pro Ala Gly Leu Ile Ala Gly Ala Ser 40

Leu Leu Met Val Ala Lys Val Gly Val Ser Met Phe Asn Arg Pro His 55

<210> 199 <211> 54 <212> PRT <213> Homo sapiens <400> 199 Glu Ile Ala Gly Tyr Gly Ala Glu Gly Phe Ser Ser Val Leu Gly Tyr 10

<210> 200 <211> 151 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 Met Ala Ala Ser Thr Ser Met Xaa Pro Val Ala Val Thr Ala Ala Val -15 Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile 1 Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu 20 Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala 35 Leu Pro Xaa Gly Gln Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp 50 Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val 70 65 Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ser Lys 85 Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile 100 Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn 110 115

Gly Lys Val Lys Ser Phe Lys

125

<210> 201

130

Phe Pro Ser Met Leu Ala Leu Ser Gly Tyr Ile Gln Ala Cys Arg Ala

30

4.5

```
Leu Met Ile Thr Ala Ile Leu Leu Gly Phe Leu Gly Leu Leu Leu Gly
            60
                            65
Ile Ala Gly Leu Arg Cys Thr Asn Ile Gly Gly Leu Glu Leu Ser Arg
         75
                 80
Lys Ala Lys Leu Ala Ala Thr Ala Gly Ala Pro His Ile Leu Ala Gly
            . 95
   9.0
                                     100
Ile Cys Gly Met Val Ala Ile Ser Trp Tyr Ala Phe Asn Ile Thr Arg
         110
   105
                          115
Asp Phe Phe Asp Pro Leu Tyr Pro Gly Thr Lys Tyr Glu Leu Gly Pro
      125 130
Ala Leu Tyr Leu Gly Trp Ser Ala Ser Leu Ile Ser Ile Leu Gly Gly
      140 145 150
Leu Cys Leu Cys Ser Ala Cys Cys Cys Gly Ser Asp Glu Asp Pro Ala
         155 160
                                165
Ala Ser Ala Arg Arg Pro Tyr Gln Ala Pro Val Ser Val Met Pro Val
                    175
                             180
Ala Thr Ser Asp Gln Glu Gly Asp Ser Ser Phe Gly Lys Tyr Gly Arg
                  190
Asn Ala Tyr Val
200
<210> 202
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<211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -47..-1 <400> 202 Met His Gly Phe Glu Ile Ile Ser Leu Lys Glu Glu Ser Pro Leu Gly -40 Lys Val Ser Gln Gly Pro Leu Phe Asn Val Thr Ser Gly Ser Ser Ser -30 -25 Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn Leu His Cys Phe -15 ~10 Pro Asp Leu Pro Thr Glu Met Pro Leu Arg Ala Lys Gly Val Asn Thr

1.0

5

<210> 203

<211> 146 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -31..-1 <400> 203 Met Met Trp Gln Lys Tyr Ala Gly Ser Arg Arg Ser Met Pro Leu Gly -25 Ala Arg Ile Leu Phe His Gly Val Phe Tyr Ala Gly Gly Phe Ala Ile -10 - 5 Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Ala Leu Tyr Tyr Lys 10 Leu Ala Val Glu Gln Leu Gln Ser His Pro Glu Ala Gln Glu Ala Leu 2.0 25 30

<210> 204 <211> 87 <212> PRT <213> Homo sapiens

<210> 205
<211> 40
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -27..-1

<400> 205
Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr
-25
-20
-15

Leu Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly
-10 -5 1 5

Leu Ser Leu Arg Ser Ala Met Ser
10

<210> 206 <211> 154 <212> PRT <213> Homo sapiens

<400> 206 Met Gly Ser Leu Ser Gly Leu Arg Leu Ala Ala Gly Ser Cys Phe Arg

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Leu Cys Glu Arg Asp Val Ser Ser Ser Leu Arg Leu Thr Arg Ser Ser
                    25
Asp Leu Lys Arg Ile Asn Gly Phe Cys Thr Lys Pro Gln Glu Ser Pro
                      40
Gly Ala Pro Ser Arg Thr Tyr Asn Arg Val Pro Leu His Lys Pro Thr
                55
Asp Trp Gln Lys Lys Ile Leu Ile Trp Ser Gly Arg Phe Lys Lys Glu
             70
Asp Glu Ile Pro Glu Thr Val Ser Leu Glu Met Leu Asp Ala Ala Lys
           85 90
Asn Lys Met Arg Val Lys Ser Ser Tyr Leu Met Ile Ala Leu Thr Val
   100 105
Val Gly Cys Ile Phe Met Val Ile Glu Gly Lys Lys Ala Ala Gln Arg
     115 120 125
His Glu Thr Leu Thr Ser Leu Asn Leu Glu Lys Lys Ala Arg Leu Lys
 130 135
Glu Glu Ala Ala Met Lys Ala Lys Thr Glu
145 150
```

<210> 207 <211> 101 <212> PRT <213> Homo sapiens

<400> 207

Met Val Cys Glu Lys Cys Glu Lys Lys Leu Gly Thr Val Ile Thr Pro 10 Asp Thr Trp Lys Asp Gly Ala Arg Asn Thr Thr Glu Ser Gly Gly Arg 20 2.5 Lys Leu Asn Lys Asn Lys Ala Leu Thr Ser Lys Lys Ala Arg Phe Asp 40 Pro Tyr Gly Lys Asn Lys Phe Ser Thr Cys Arg Ile Cys Lys Ser Ser 5.5 60 Val His Gln Pro Gly Ser His Tyr Cys Gln Gly Cys Ala Tyr Lys 70 75 Gly Ile Cys Ala Met Cys Gly Lys Lys Val Leu Asp Thr Lys Asn Tyr 90 Lys Gln Thr Ser Val 100

<210> 208 <211> 456 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1 <400> 208

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35
Glu Glu Glu Glu Glu Arg Lys Lys Cys Pro Lys Lys Ala Ser
45 50 55
Phe Ala Ser Ala Ser Ala Glu Val Gly Lys Lys Lys Lys Cys
60 65 70
Gln Lys Gln Gly Pro Pro Cys Ser Asp Ser Glu Glu Glu Val Glu Arg
     80 85 90
Lys Lys Lys Cys His Lys Gln Ala Leu Val Gly Ser Asp Ser Ala Glu
        95 100 105
Asp Glu Lys Arg Lys Arg Lys Cys Gln Lys His Ala Pro Ile Asn Ser
       110 115 120
Ala Gln His Leu Asp Asn Val Asp Gln Thr Gly Pro Lys Ala Trp Lys
    125 130 135
Gly Ser Thr Thr Asn Asp Pro Pro Lys Gln Ser Pro Gly Ser Thr Ser
 140 145 150
Pro Lys Pro Pro His Thr Leu Ser Arg Lys Gln Trp Arg Asn Arg Gln
155 160 165 170
Lys Asn Lys Arg Arg Cys Lys Asn Lys Phe Gln Pro Pro Gln Val Pro
    175 180 185
Asp Gln Ala Pro Ala Glu Ala Pro Thr Glu Lys Thr Glu Val Ser Pro
  190 195 200
Val Pro Arg Thr Asp Ser His Gly Ala Arg Ala Gly Ala Leu Arg Ala
 205 210 215
Arg Met Ala Gln Arg Leu Asp Gly Ala Arg Phe Arg Tyr Leu Asn Glu
                     230
  220 225
Gln Leu Tyr Ser Gly Pro Ser Ser Ala Ala Gln Arg Leu Phe Gln Glu
235 240 245 250
Asp Pro Glu Ala Phe Leu Leu Tyr His Arg Gly Phe Gln Ser Gln Val
   255 260 265
Lys Lys Trp Pro Leu Gln Pro Val Asp Arg Ile Ala Arg Asp Leu Arg
  270 275 280
Gln Arg Pro Ala Ser Leu Val Val Ala Asp Phe Gly Cys Gly Asp Cys
 285 290 295
Arg Leu Ala Ser Ser Ile Arg Asn Pro Val His Cys Phe Asp Leu Ala
  300 305 310
Ser Leu Asp Pro Arg Val Thr Val Cys Asp Met Ala Gln Val Pro Leu
315 320 335
Glu Asp Glu Ser Val Asp Val Ala Val Phe Cys Leu Ser Leu Met Gly
                        340 345
    335
Thr Asn Ile Arg Asp Phe Leu Glu Glu Ala Asn Arg Val Leu Lys Pro
                    355 360
       350
Gly Gly Leu Leu Lys Val Ala Glu Val Ser Ser Arg Phe Glu Asp Val
    365 370 375
Arg Thr Phe Leu Arg Ala Val Thr Lys Leu Gly Phe Lys Ile Val Ser
  380 385 390
Lys Asp Leu Thr Asn Ser His Phe Phe Leu Phe Asp Phe Gln Lys Thr
395 400 405 410
Gly Pro Pro Leu Val Gly Pro Lys Ala Gln Leu Ser Gly Leu Gln Leu
                       420
     415
Gln Pro Cys Leu Tyr Lys Arg Arg
        430
```

<210> 209 <211> 98 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -17..-1

```
<400> 209
Met Pro Ser Ser Phe Phe Leu Leu Leu Gln Phe Phe Leu Arg Ile Asp
    -15 -10
Gly Val Leu Ile Arg Met Asn Asp Thr Arg Leu Tyr His Glu Ala Asp
                                10 15
Lys Thr Tyr Met Leu Arg Glu Tyr Thr Ser Arg Glu Ser Lys Ile Ser
                    25
          2.0
Ser Leu Met His Val Pro Pro Ser Leu Phe Thr Glu Pro Asn Glu Ile
       35
                         40
Ser Gln Tyr Leu Pro Ile Lys Glu Ala Val Cys Glu Lys Leu Ile Phe
     50 55
                              60
Pro Glu Arg Ile Asp Pro Asn Pro Ala Asp Ser Gln Lys Ser Thr Gln
Val Glu
80
<210> 210
<211> 83
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -29..-1
<400> 210
Met Thr Leu Leu Ser Phe Ala Ala Phe Thr Ala Ala Phe Ser Val Leu
            -25 -20 -15
Pro Cys Tyr Tyr Leu Gly Leu Phe Gln Arg Ala Leu Ala Ser Val Phe
         -10 -5
Asp Pro Leu Cys Val Cys Ser Arg Val Leu Pro Thr Pro Val Cys Thr
                  10
Leu Val Ala Thr Gln Ala Glu Lys Ile Leu Glu Asn Gly Pro Cys Pro
20 25
                    30
Thr Lys Glu Ala Ala Gln Leu Val Gly Lys Gly Ser Val Ser Ala Arg
Asn Ala Ser
<210> 211
<211> 229
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 211
Met Gly Asp Lys Ile Trp Leu Pro Phe Pro Val Leu Leu Leu Ala Ala
      -20 -15 -10
Leu Pro Pro Val Leu Leu Pro Gly Ala Ala Gly Phe Thr Pro Ser Leu
   -5
                     1
Asp Ser Asp Phe Thr Phe Thr Leu Pro Ala Gly Gln Lys Glu Cys Phe
10 15 20
Tyr Gln Pro Met Pro Leu Lys Ala Ser Leu Glu Ile Glu Tyr Gln Val
      30 35 40
```

Leu Asp Gly Ala Gly Leu Asp Ile Asp Phe His Leu Ala Ser Pro Glu

45 5.0 Gly Lys Thr Leu Val Phe Glu Gln Arg Lys Ser Asp Gly Val His Thr 60 65 70 Val Glu Thr Glu Val Gly Asp Tyr Met Phe Cys Phe Asp Asn Thr Phe 75 80 ser Thr Ile Ser Glu Lys Val Ile Phe Phe Glu Leu Ile Leu Asp Asn 90 95 100 105 Met Gly Glu Gln Ala Gln Glu Gln Glu Asp Trp Lys Lys Tyr Ile Thr 110 115 120 Gly Thr Asp Ile Leu Asp Met Lys Leu Glu Asp Ile Leu Glu Ser Ile 125 130 135 Ser Ser Ile Lys Ser Arg Leu Ser Lys Ser Gly His Ile Gln Ile Leu 140 145 150 Leu Arg Ala Phe Glu Ala Arg Asp Arg Asn Ile Gln Glu Ser Asn Phe 155 160 165 Asp Arg Val Asn Phe Trp Ser Met Val Asn Leu Val Val Met Val Val 170 175 180 185 Val Ser Ala Ile Gln Val Tyr Met Leu Lys Ser Leu Phe Glu Asp Lys 190 195 Arg Lys Ser Arg Thr 205

<210> 212 <211> 152 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1

<400> 212

Val Tyr Tyr Arg Gly Gly Ala Leu Leu Thr Ser Thr Ser Gly Pro Gly

15 20 25

Phe His Leu Met Leu Pro Phe Ile Thr Ser Tyr Lys Ser Val Gln Thr 30 35 40

Thr Leu Gln Thr Asp Glu Val Lys Asn Val Pro Cys Gly Thr Ser Gly
45 50 55

Gly Val Met Ile Tyr Phe Asp Arg Ile Glu Val Val Asn Phe Leu Val
60 65 70 75

Pro Asn Ala Val His Asp Ile Val Lys Asn Tyr Thr Ala Asp Tyr Asp 80 85 90

Lys Ala Leu Ile Phe Asn Lys Ile His His Glu Leu Asn Gln Phe Cys 95 100 105

Ser Val His Thr Leu Gln Glu Val Tyr Ile Glu Leu Phe Gly Leu Glu 110 115 120

Asn Asp Phe Ser Gln Glu Ser Ser 125 130

<210> 213 <211> 179

<212> PRT

<213 > Homo sapiens

<220>

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<221> SIGNAL
<222> -54..-1
<400> 213
Met Ala Ala Ser Glu Ala Ala Val Val Ser Ser Pro Ser Leu Lys Thr
         -50 -45 -40
Asp Thr Ser Pro Val Leu Glu Thr Ala Gly Thr Val Ala Ala Met Ala
             -30
         ~35
Ala Thr Pro Ser Ala Arg Ala Ala Ala Ala Val Val Ala Ala Ala Ala
 -20 -15 -10
Arg Thr Gly Ser Glu Ala Arg Val Ser Lys Ala Ala Leu Ala Thr Lys
 <sup>-5</sup> 1 5
Leu Leu Ser Leu Ser Gly Val Phe Ala Val His Lys Pro Lys Gly Pro
                20
          15
Thr Ser Ala Glu Leu Leu Asn Arg Leu Lys Glu Lys Leu Leu Ala Glu
            35
Ala Gly Met Pro Ser Pro Glu Trp Thr Lys Arg Lys Lys Gln Thr Leu
          50
Lys Ile Gly His Gly Gly Thr Leu Asp Ser Ala Ala Arg Gly Val Leu
                  65
Val Val Gly Ile Gly Ser Gly Thr Lys Met Leu Thr Ser Met Leu Ser
                     85 90
Gly Ser Lys Arg Tyr Thr Ala Ile Gly Glu Leu Gly Lys Ala Thr Asp
                         100 105
Thr Leu Asp Ser Thr Gly Lys Val Thr Glu Glu Lys Pro Tyr Gly Met
             115
Asn Leu Ile
     125
```

-40 -35 Val His Ser Ser Met Asn Glu Met Leu Glu Glu Gly His Glu Tyr Ala -20 -15 Val Met Leu Tyr Thr Trp Arg Ser Cys Ser Arg Ala Ile Pro Gln Val - 5 Lys Cys Asn Glu Gln Pro Asn Arg Val Glu Ile Tyr Glu Lys Thr Val 10 15 Glu Val Leu Glu Pro Glu Val Thr Lys Leu Met Lys Phe Met Tyr Phe 25 30 Gln Arg Lys Ala Ile Glu Arg Phe Cys Ser Glu Val Lys Arg Leu Cys 4.5 His Ala Glu Arg Arg Lys Asp Phe Val Ser Glu Ala Tyr Leu Leu Thr 60

Leu Gly Lys Phe Ile Asn Met Phe Ala Val Leu Asp Glu Leu Lys Asn 75 Met Lys Cys Ser Val Lys Asn Asp His Ser Ala Tyr Lys Arg Ala Ala 95 90 Gln Phe Leu Arg Lys Met Ala Asp Pro Gln Ser Ile Gln Glu Ser Gln 110 115 105 Asn Leu Ser Met Phe Leu Ala Asn His Asn Arg Ile Thr Gln Cys Leu 120 125 130 His Gln Gln Leu Glu Val Ile Pro Gly Tyr Glu Glu Leu Leu Ala Asp 140 Ile Val Asn Ile Cys Val Asp Tyr Tyr Glu Asn Lys Met Tyr Leu Thr 150 155 Pro Ser Glu Lys His Met Leu Leu Lys Val Lys Leu Pro 165 170 175

<210> 215 <211> 135 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -22..-1

<400> 215 Met Gln Thr Val Tyr Tyr Gly Ser Leu Gly Leu Trp Leu Ala Leu Val -15 Asp Gly Leu Val Arg Ser Ser Pro Ser Leu Asp Gln Met Phe Asp Ala Glu Ile Leu Gly Phe Ser Thr Pro Pro Gly Arg Leu Ser Met Met Ser 20 **1**5 Phe Ile Phe Asn Ala Leu Thr Cys Ala Leu Gly Leu Leu Tyr Phe Ile 35 Arg Arg Gly Lys Gln Cys Leu Asp Phe Thr Val Thr Val His Phe Phe 50 His Leu Leu Gly Cys Trp Phe Tyr Ser Ser Arg Phe Pro Ser Ala Leu 65 Thr Trp Trp Leu Val Gln Ala Val Cys Ile Ala Leu Met Ala Val Ile 85 90 80 Gly Glu Tyr Leu Cys Met Arg Thr Glu Leu Lys Glu Ile Pro Leu Asn 95 100 Ser Ala Pro Lys Ser Asn Val 110

<210 > 216 <211 > 67 <212 > PRT <213 > Homo sapiens <220 > <221 > SIGNAL <222 > -38..-1

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<210> 217

<211> 125 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -54..-1 <400> 217 Met Ala Asp Glu Glu Leu Glu Ala Leu Arg Arg Gln Arg Leu Ala Glu -50 -45 Leu Gln Ala Lys His Gly Asp Pro Gly Asp Ala Ala Gln Gln Glu Ala -35 -30 -25 Lys His Arg Glu Ala Glu Met Arg Asn Ser Ile Leu Ala Gln Val Leu -20 -15 -10 Asp Gln Ser Ala Arg Ala Arg Leu Ser Asn Leu Ala Leu Val Lys Pro 1 5 Glu Lys Thr Lys Ala Val Glu Asn Tyr Leu Ile Gln Met Ala Arg Tyr 15 20 Gly Gln Leu Ser Glu Lys Val Ser Glu Gln Gly Leu Ile Glu Ile Leu 30 35 Lys Lys Val Ser Gln Gln Thr Glu Lys Thr Thr Thr Val Lys Phe Asn 50 Arg Arg Lys Val Met Asp Ser Asp Glu Asp Asp Asp Tyr 65

<210> 218 <211> 376 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -21..-1 <400> 218 Met Gly His Arg Phe Leu Arg Gly Leu Leu Thr Leu Leu Leu Pro Pro -10 -15 Pro Pro Leu Tyr Thr Arg His Arg Met Leu Gly Pro Glu Ser Val Pro <del>-</del> 5 1 5 Pro Pro Lys Arg Ser Arg Ser Lys Leu Met Ala Pro Pro Arg Ile Gly 15 20 Thr His Asn Gly Thr Phe His Cys Asp Glu Ala Leu Ala Cys Ala Leu 35 Leu Arg Leu Leu Pro Glu Tyr Arg Asp Ala Glu Ile Val Arg Thr Arg 50 Asp Pro Glu Lys Leu Ala Ser Cys Asp Ile Val Val Asp Val Gly Gly 65 70 Glu Tyr Asp Pro Arg Arg His Arg Tyr Asp His His Gln Arg Ser Phe

Thr Glu Thr Met Ser Ser Leu Ser Pro Gly Arg Pro Trp Gln Thr Lys

```
100
Leu Ser Ser Ala Gly Leu Ile Tyr Leu His Phe Gly His Lys Leu Leu
                       115
                           . 120
Ala Gln Leu Leu Gly Thr Ser Glu Glu Asp Ser Met Val Gly Thr Leu
                   130
                                    135
Tyr Asp Lys Met Tyr Glu Asn Phe Val Glu Glu Val Asp Ala Val Asp
                                 150
                145
Asn Gly Ile Ser Gln Trp Ala Glu Gly Glu Pro Arg Tyr Ala Leu Thr
                             165
             160
Thr Thr Leu Ser Ala Arg Val Ala Arg Leu Asn Pro Thr Trp Asn His
                        180 185
Pro Asp Gln Asp Thr Glu Ala Gly Phe Lys Arg Ala Met Asp Leu Val
                                200
                      195
Gln Glu Glu Phe Leu Gln Arg Leu Asp Phe Tyr Gln His Ser Trp Leu
           210
                                    215
Pro Ala Arg Ala Leu Val Glu Glu Ala Leu Ala Gln Arg Phe Gln Val
       225
                                 230
Asp Pro Ser Gly Glu Ile Val Glu Leu Ala Lys Gly Ala Cys Pro Trp
                              245
             240
Lys Glu His Leu Tyr His Leu Glu Ser Gly Leu Ser Pro Pro Val Ala
                         260
         255
Ile Phe Phe Val Ile Tyr Thr Asp Gln Ala Gly Gln Trp Arg Ile Gln
                       275
      270
Cys Val Pro Lys Glu Pro His Ser Phe Gln Ser Arg Leu Pro Leu Pro
        290
                                   295
Glu Pro Trp Arg Gly Leu Arg Asp Glu Ala Leu Asp Gln Val Ser Gly
                                 310
                305
Ile Pro Gly Cys Ile Phe Val His Ala Ser Gly Phe Ile Gly Gly His
             320 325 . 330
Arg Thr Arg Glu Gly Ala Leu Ser Met Ala Arg Ala Thr Leu Ala Gln
         335
                 340
Arq Ser Tyr Leu Pro Gln Ile Ser
                      355
    350
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<210> 219

<211> 211

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -30..-1

<400> 219 Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val -25 -20 -15 Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro - 5 -10 Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu 10 Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu 25 Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly 45 40 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 60 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Val Pro Arg Met 75 70 Glu Glu Lys Glu Ala Leu Val Pro Ile Gln Lys Ala Thr Asp Ser Phe

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<211> 154
<212> PRT
<213> Homo sapiens
<220>
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<222> -60..-1
<400> 220
Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu
           -55 -50
Arg Gln Arg Arg Gln Lys Leu Leu Ala Gln Leu His His Arg Lys
              -40
                                 -35
Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu
                             -20
Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln
                         - 5
Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln
                  10
                                    15
Ala Leu Leu Arg Val Tyr Val Ile Gln Glu Gln Ala Thr Val Lys Leu
                                 3.0
Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met
                             4.5
Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Glu Ser Ser Leu Ala Phe
                         60
Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln
                     75
Pro Glu Phe His Ile Glu Ile Leu Ser Ile
```

Ala Val Ser Leu Ser Ala Pro Ala Phe Ala Ser Ala Leu Arg Ser Met
-10
Lys Ser Ser Gln Ala Ala Arg Lys Asp Asp Phe Leu Arg Ser Leu Ser
10
Asp Gly Asp Ser Gly Thr Ser Glu His Ile Ser Ala Val Val Thr Ser
25
Pro Arg Ile Ser Cys His Gly Ala Ala Ile Pro Thr Ala Arg Ala Leu
40
Cys Leu Gly Cys Ser Cys Cys Thr Glu Arg Leu Leu Leu Pro Pro
55
Ser Leu Leu Ser Leu Glu Ala Pro Ala Ser Thr
75

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<210> 222
<211> 346
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 222
Met Ala Met Ala Gln Lys Leu Ser His Leu Leu Pro Ser Leu Arg Gln
                 -10
             -15
Val Ile Gln Glu Pro Gln Leu Ser Leu Gln Pro Glu Pro Val Phe Thr
              5
Val Asp Arg Ala Glu Val Pro Pro Leu Phe Trp Lys Pro Tyr Ile Tyr
       20
Ala Gly Tyr Arg Pro Leu His Gln Thr Trp Arg Phe Tyr Phe Arg Thr
                                 40
             35
Leu Phe Gln Gln His Asn Glu Ala Val Asn Val Trp Thr His Leu Leu
            50 55
Ala Ala Leu Val Leu Leu Leu Arg Leu Ala Leu Phe Val Glu Thr Val
                          70
Asp Phe Trp Gly Asp Pro His Ala Leu Pro Leu Phe Ile Ile Val Leu
                      8.5
Ala Ser Phe Thr Tyr Leu Ser Leu Ser Ala Leu Ala His Leu Leu Gln
                100
                                 105
Ala Lys Ser Glu Phe Trp His Tyr Ser Phe Phe Phe Leu Asp Tyr Val
               115 120
Gly Val Ala Val Tyr Gln Phe Gly Ser Ala Leu Ala His Phe Tyr Tyr
                             135
            130
Ala Ile Glu Pro Ala Trp His Ala Gln Val Gln Ala Val Phe Leu Pro
                                          155
              150
       145
Met Ala Ala Phe Leu Ala Trp Leu Ser Cys Ile Gly Ser Cys Tyr Asn
                                       170
                      165
Lys Tyr Ile Gln Lys Pro Gly Leu Leu Gly Arg Thr Cys Gln Glu Val
                                    185
   175 180
Pro Ser Val Leu Ala Tyr Ala Leu Asp Ile Ser Pro Val Val His Arg
                     200
190 195
Ile Phe Val Ser Ser Asp Pro Thr Thr Asp Asp Pro Ala Leu Leu Tyr
             210 215
His Lys Cys Gln Val Val Phe Phe Leu Leu Ala Ala Phe Phe Ser
         225 230
Thr Phe Met Pro Glu Arg Trp Phe Pro Gly Ser Cys His Val Phe Gly
                      245
Gln Gly His Gln Leu Phe His Ile Phe Leu Val Leu Cys Thr Leu Ala
```

255 260 265

Gln Leu Glu Ala Val Ala Leu Asp Tyr Glu Ala Arg Arg Pro Ile Tyr

<210> 223 <211> 210 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -20..-1 <400> 223 Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser - 15 -10 Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp 1 Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys 20 Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr 35 Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg 55 5.0 Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg 70 65 Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr 85 Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly 100 Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro 115 120 Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys 130 135 Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu 145 150 His Leu Leu Ala Val Thr Lys Glu Ser Met Leu Pro Ala Gly Ala Glu 165 160 Ser Lys His Thr Ala Thr Pro Ala His Ala Cys Val Gln Thr Gly Lys Pro Lys

<210> 224 <211> 184 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -20..-1

190

<400> 224
Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser

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```
-15
                                       -10
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
Asn Asp Ala Pro Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Arg Arg
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
Thr Glu Ser Phe Asp Val Val Thr Lys Cys Val Ser Phe Thr Leu Thr
                               85
Glu Gln Phe Met Glu Lys Phe Val Asp Pro Gly Asn His Asn Ser Gly
                           100
Ile Asp Leu Leu Arg Thr Tyr Leu Trp Arg Cys Gln Phe Leu Leu Pro
                      115
Phe Val Ser Leu Gly Leu Met Cys Phe Gly Ala Leu Ile Gly Leu Cys
            130
                                      135
Ala Cys Ile Cys Arg Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu
              145
                                  150
His Leu Leu Ala Asp Thr Met Leu
          160
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<210> 225 <211> 227 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1 <400> 225

Met Gly Trp Thr Met Arg Leu Val Thr Ala Ala Leu Leu Leu Gly Leu -15 Met Met Val Val Thr Gly Asp Glu Asp Glu Asn Ser Pro Cys Ala His Glu Ala Leu Leu Asp Glu Asp Thr Leu Phe Cys Gln Gly Leu Glu Val 20 Phe Tyr Pro Glu Leu Gly Asn Ile Gly Cys Lys Val Val Pro Asp Cys Asn Asn Tyr Arg Gln Lys Ile Thr Ser Trp Met Glu Pro Ile Val Lys 50 Phe Pro Gly Ala Val Asp Gly Ala Thr Tyr Ile Leu Val Met Val Asp Pro Asp Ala Pro Ser Arg Ala Glu Pro Arg Gln Arg Phe Trp Arg His 80 Trp Leu Val Thr Asp Ile Lys Gly Ala Asp Leu Lys Lys Gly Lys Ile 100 Gln Gly Gln Glu Leu Ser Ala Tyr Gln Ala Pro Ser Pro Pro Ala His 115 Ser Gly Phe His Arg Tyr Gln Phe Phe Val Tyr Leu Gln Glu Gly Lys 125 130 Val Ile Ser Leu Leu Pro Lys Glu Asn Lys Thr Arg Gly Ser Trp Lys 145 150 Met Asp Arg Phe Leu Asn Arg Phe His Leu Gly Glu Pro Glu Ala Ser 160 Thr Gln Phe Met Thr Gln Asn Tyr Gln Asp Ser Pro Thr Leu Gln Ala 175 180

```
Pro Arg Glu Arg Ala Ser Glu Pro Lys His Lys Asn Gln Ala Glu Ile
                                              200
                             195
Ala Ala Cys
    205
<210> 226
<211> 74
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -41..-1
<400> 226
Met Ile Ala Arg Arg Asn Pro Val Pro Leu Arg Phe Leu Pro Asp Glu
          -35 -30
Ala Arg Ser Leu Pro Pro Pro Lys Leu Thr Asp Pro Arg Leu Leu Tyr
                  -20
                                     -15
Ile Gly Phe Leu Gly Tyr Cys Ser Gly Leu Ile Asp Asn Leu Ile Arg
              - 5
                               1
Arg Arg Pro Ile Ala Thr Ala Gly Leu His Arg Gln Leu Leu Tyr Ile
                      15
Thr Ala Phe Phe Leu Leu Asp Ile Ile Leu
<210> 227
<211> 73
<212> PRT
<213> Homo sapiens
<400> 227
Met Glu Lys Tyr Glu Asn Leu Gly Leu Val Gly Glu Gly Ser Tyr Gly
                                 10
Met Val Met Lys Cys Arg Asn Lys Asp Thr Gly Arg Ile Val Ala Ile
          20
                              25
Lys Lys Phe Leu Glu Ser Asp Asp Lys Met Val Lys Lys Ile Ala
Met Arg Glu Val Lys Leu Leu Lys Gln Leu Arg His Glu Asn Leu Val
                     55
Asn Leu Leu Glu Val Cys Lys Lys
<210> 228
<211> 82
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 228
Met Lys Arg Leu Leu Pro Ala Thr Ser Leu Ala Gly Pro Val Leu Ser
         -10
```

Thr Leu Ile Ala Pro Thr Pro Met Leu Phe Cys Glu Asp Lys Ser Trp

10 15 Asp Leu Phe Leu Phe Phe Lys Ser His Lys Thr Trp Gly Ile Ser Thr 20 25 Asn Leu Ser Ser Cys Pro Phe Gly Asn Leu Phe Leu Cys Val Gln Phe 40 45 Val Arg Glu Lys Gln Ser Phe Cys Met Asn Thr Glu Cys Asp Leu Arg 55 Lys Asn 65

<210> 229 <211> 119 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -56..-1 <400> 229 Met Ala Glu Pro Ser Ala Ala Thr Gln Ser His Ser Ile Ser Ser -55 -50 -45 Ser Phe Gly Ala Glu Pro Ser Ala Pro Gly Gly Gly Ser Pro Gly -40 -35 -30 Ala Cys Pro Ala Leu Gly Thr Lys Ser Cys Ser Ser Ser Cys Ala Asp -20 -15 -10 Ser Phe Val Ser Ser Ser Ser Gln Pro Val Ser Leu Phe Ser Thr <del>-</del> 5 1 Ser Gln Glu Gly Leu Ser Ser Leu Cys Ser Asp Glu Pro Ser Ser Glu 10 15 20 Ile Met Thr Ser Ser Phe Leu Ser Ser Ser Glu Ile His Asn Thr Gly

Leu Thr Ile Leu His Gly Glu Lys Ser His Val Leu Gly Ser Gln Pro 50

<210> 230 <211> 54 <212> PRT <213> Homo sapiens <400> 230

25 30 35

4.5

Ile Leu Ala Lys Lys Lys 60

Ala Phe Val Trp Glu Pro Ala Met Val Arg Ile Asn Ala Leu Thr Ala 5 10 Ala Ser Glu Ala Ala Cys Leu Ile Val Ser Val Asp Glu Thr Ile Lys 25 Asn Pro Arg Ser Thr Val Asp Ala Pro Thr Ala Ala Gly Arg Gly Arg 35 40 Gly Arg Gly Arg Pro His 50

<210> 231 <211> 210 <212> PRT

<213> Homo sapiens

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<220>
<221> SIGNAL
<222> -14..-1
<400> 231
Met Leu Thr Leu Leu Gly Leu Ser Phe Ile Leu Ala Gly Leu Ile Val
                                 - 5
               -10
Gly Gly Ala Cys Ile Tyr Lys Tyr Phe Met Pro Lys Ser Thr Ile Tyr
                         10
Arg Gly Glu Met Cys Phe Phe Asp Ser Glu Asp Pro Ala Asn Ser Leu
                      25
Arg Gly Gly Glu Pro Asn Phe Leu Pro Val Thr Glu Glu Ala Asp Ile
                  40
                                     45
Arg Glu Asp Asp Asn Ile Ala Ile Ile Asp Val Pro Val Pro Ser Phe
                                 6.0
Ser Asp Ser Asp Pro Ala Ala Ile Ile His Asp Phe Glu Lys Gly Met
                             75
Thr Ala Tyr Leu Asp Leu Leu Gly Ile Cys Tyr Leu Met Pro Leu
                         90
Asn Thr Ser Ile Val Met Pro Pro Lys Asn Leu Val Glu Leu Phe Gly
                      105
                                        110
Lys Leu Ala Ser Gly Arg Tyr Leu Pro Gln Thr Tyr Val Val Arg Glu
                                    125
                 120
Asp Leu Val Ala Val Glu Glu Ile Arg Asp Val Ser Asn Leu Gly Ile
              135
                                140
Phe Ile Tyr Gln Leu Cys Asn Asn Arg Lys Ser Phe Arg Leu Arg Arg
                             155
Arg Asp Leu Leu Gly Phe Asn Lys Arg Ala Ile Asp Lys Cys Trp
      165 170
                                            175
Lys Ile Arg His Phe Pro Asn Glu Phe Ile Val Glu Thr Lys Ile Cys
            185
Gln Glu
195
```

<210> 232 <211> 108 <212> PRT <213> Homo sapiens

<400> 232

 Met
 Gly
 Cys
 Val
 Phe
 Gln
 Ser
 Thr
 Glu
 Asp
 Lys
 Cys
 Ile
 Phe
 Lys
 Ile

 Asp
 Trp
 Thr
 Leu
 Ser
 Pro
 Gly
 Glu
 His
 Ala
 Lys
 Asp
 Glu
 Tyr
 Val
 Leu
 July
 Asp
 Glu
 Tyr
 Val
 Leu
 Ser
 Val
 Pro
 Ile
 Gly
 Asp
 Glu
 Asp
 Glu
 Asp
 Asp
 Glu
 Thr
 Tyr
 Tyr
 Ile
 Leu
 Leu
 Asp
 Glu
 Asp
 Glu
 Asp
 Glu
 Asp
 Glu
 Asp
 Glu
 Asp
 Glu
 Tyr
 Tyr
 Ile
 Cys
 Glu
 Ile
 Leu
 Leu
 Leu
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 Leu
 Leu
 Leu
 Leu
 Leu
 Leu

<210> 233 <211> 43

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -18..-1
<400> 233
Met Ser Ser Gly Arg Leu Arg Trp Leu Met Pro Val Ile Pro Ala Leu
     -15
                   -10
Trp Gly Ala Glu Lys Gly Glu Ser Pro Glu Val Ser Ser Phe Glu Thr
Arg Leu Ala Asn Met Ala Lys Pro Cys Leu Tyr
15 20
<210> 234
<211> 36
<212> PRT
<213> Homo sapiens
<400> 234
Met Ser Ala Arg Ile Pro Phe Tyr Lys Asp Thr Ser Gln Ile Arg Leu
                                 10
Gly Ser Thr Ile Ile Pro His Phe Asn Leu Ile Thr Phe Val Lys Thr
        20
                       25
Phe Phe Gln Ile
     35
<210> 235
<211> 307
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -13..-1
<400> 235
Met Leu Ala Val Ser Leu Thr Val Pro Leu Leu Gly Ala Met Met Leu
       -10
                           - 5
Leu Glu Ser Pro Ile Asp Pro Gln Pro Leu Ser Phe Lys Glu Pro Pro
                     10
Leu Leu Gly Val Leu His Pro Asn Thr Lys Leu Arg Gln Ala Glu
                                    30
Arg Leu Phe Glu Asn Gln Leu Val Gly Pro Glu Ser Ile Ala His Ile
                                 45
Gly Asp Val Met Phe Thr Gly Thr Ala Asp Gly Arg Val Val Lys Leu
                             60
Glu Asn Gly Glu Ile Glu Thr Ile Ala Arg Phe Gly Ser Gly Pro Cys
Lys Thr Arg Asp Asp Glu Pro Val Cys Gly Arg Pro Leu Gly Ile Arg
                     90
Ala Gly Pro Asn Gly Thr Leu Phe Val Ala Asp Ala Cys Lys Gly Leu
                  105
                                     110
Phe Glu Val Asn Pro Trp Lys Arg Glu Val Lys Leu Leu Ser Ser
```

125

Glu Thr Pro Ile Glu Gly Lys Asn Met Ser Phe Val Asn Asp Leu Thr

140

120

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```
Val Ser Gln Asp Gly Arg Lys Ile Tyr Phe Thr Asp Ser Ser Ser Lys
                     155
Trp Gln Arg Arg Asp Tyr Leu Leu Leu Val Met Glu Gly Thr Asp Asp
                          175
        170
Gly Arg Leu Leu Glu Tyr Asp Thr Val Thr Arg Glu Val Lys Val Leu
      185
                      190
Leu Asp Gln Leu Arg Phe Pro Asn Gly Val Gln Leu Ser Pro Ala Glu
      200 205
Asp Phe Val Leu Val Ala Glu Thr Thr Met Ala Arg Ile Arg Arg Val
        215 220
Tyr Val Ser Gly Leu Met Lys Gly Gly Ala Asp Leu Phe Val Glu Asn
                    235 240
Met Pro Gly Phe Pro Asp Asn Ile Arg Pro Ser Ser Ser Gly Gly Tyr
                  250 255
Trp Val Gly Met Ser Thr Ile Arg Pro Asn Pro Gly Phe Ser Met Leu
      265
                      270
Asp Phe Leu Ser Glu Arg Pro Trp Ile Lys Arg Met Ile Phe Lys Ala
           280
                    285
Lys Lys Lys
<210> 236
<211> 106
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<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -32..-1 <400> 236 Met Phe Ala Pro Ala Val Met Arg Ala Phe Arg Lys Asn Lys Thr Leu - 25 Gly Tyr Gly Val Pro Met Leu Leu Leu Ile Val Gly Gly Ser Phe Gly -10 **-** 5 Leu Arg Glu Phe Ser Gln Ile Arg Tyr Asp Ala Val Lys Ser Lys Met 10 Asp Pro Glu Leu Glu Lys Lys Leu Lys Glu Asn Lys Ile Ser Leu Glu 25 Ser Glu Tyr Glu Lys Ile Lys Asp Ser Lys Phe Asp Asp Trp Lys Asn 40 Ile Arg Gly Pro Arg Pro Trp Glu Asp Pro Asp Leu Leu Gln Gly Arg 55 Asn Pro Glu Ser Leu Lys Thr Lys Thr Thr 7.0

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```
1
                                           10
 Gln Leu Ser Asp Lys Val His Asn Asp Ile
              20
<210> 238
<211> 117
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 238
Met Asp Asn Arg Phe Ala Thr Ala Phe Val Ile Ala Cys Val Leu Ser
            -15
                          -10
Leu Ile Ser Thr Ile Tyr Met Ala Ala Ser Ile Gly Thr Asp Phe Trp
Tyr Glu Tyr Arg Ser Pro Val Gln Glu Asn Ser Ser Asp Leu Asn Lys
       15
                      20
Ser Ile Trp Asp Glu Phe Ile Ser Asp Glu Ala Asp Glu Lys Thr Tyr
                  35
Asn Asp Ala Leu Phe Arg Tyr Asn Gly Thr Val Gly Leu Trp Gly Arg
               50 ... 55
Cys Ile Thr Ile Pro Lys Asn Met His Trp Tyr Ser Pro Pro Glu Arg
                               70
Thr Gly Ile Ser Leu Ile Leu Thr Ser Val Phe Phe Thr Trp Leu Ile
                  85
Ile Asp Lys Thr Thr
      95
<210> 239
<211> 178
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 239
Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe
                         -30
Gln His Xaa Xaa Ala Xaa Xaa Leu Leu Val Phe Asn Phe Leu Leu Ile
                     -15
                                    -10
Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe
                 1
Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Ile Met Gly Leu
                            20
Ile Ser Arg Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Thr Val
                        3.5
Cys Asp Cys Val Lys Leu Thr Phe Ser Pro Pro Thr Leu Leu Val Asn
                  50
                            55
Val Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln
               65
                                  70 75
```

His Asn Ile Asn Pro His Gln Gly Asn Ala Ile Leu Glu Lys Met Thr

Phe Asp Pro Glu Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe

```
100
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly
                                120
 110
           115
Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
 125 130
Ile Gly
140
<210> 240
<211> 126
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -27..-1
<400> 240
Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly Val Val
                                          -15
                         -20
Val Leu Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr Glu Ser
                                      1
                     - 5
Met Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Ile Phe Ile
                               15
             10
Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr Met Ala
                            30
          2.5
Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr
                        45
Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met Lys Gly
                                      65
                     60
Leu Lys Cys Arg Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro
                 75
                                   80
Tyr Phe Lys Met His Lys Pro Val Thr Met Lys Lys Lys
              90
<210> 241
<211> 174
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -115..-1
<400> 241
Met Arg Trp Ser Cys Glu His Leu Val Met Val Trp Ile Asn Ala Phe
-115 -100 -105
Val Met Leu Thr Thr Gln Leu Leu Pro Ser Lys Tyr Cys Asp Leu Leu
             - 95
                                -90
```

 Met Arg Trp Ser Cys
 Glu His Leu Val Met Val Trp Ile Asn Ala Phe -115
 -110
 -105
 -100

 Val Met Leu Thr Thr Gln Leu Leu Pro Ser Lys Tyr Cys Asp Leu Leu -95
 -90
 -85
 Leu Glu His Gly -85

 His Lys Ser Ala Ala His Leu Gly Lys Trp Gln Lys Leu Glu His Gly -80
 -75
 -70
 Ser Tyr Ser Asn Ala Pro Gln His Ile Trp Ser Glu Asn Thr Ile Trp -65

 Pro Gln Gly Val Leu Val Arg His Ser Arg Cys Leu Tyr Arg Ala Met -50
 -45
 -40

 Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg Phe -35
 -30
 -25

 Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile Leu

-15

```
Ile Glu Gly Gly Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg Ser
                 5
            1
Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys Asn
             20
                                2.5
Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Ile Val Leu Gly Arg
             3.5
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Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu Lys Ala Asn
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               Met Pro Ser Val Asn Ser Ala Gly Leu Cys Val
                                     -15
                  -20
ttg cag ttg aca acg gca gtr acc agt gcc ttt tta cta gca aaa gtg
                                                                   98
Leu Gln Leu Thr Thr Ala Val Thr Ser Ala Phe Leu Leu Ala Lys Val
               -5
                                 1
aat cct ttc gaa rct ttt ctc tca agg ggc ttt tgg cta tgt gcc
                                                                  146
Asn Pro Phe Glu Xaa Phe Leu Ser Arg Gly Phe Trp Leu Cys Ala Ala
                           15
cat cat ttc att cat cct tgc ctg gat tgagacgtgt tcctgattca
                                                                  193
His His Phe Ile His Pro Cys Leu Asp
aagtgttacc tcaagaagca gaagaagaaa acagactcct gatagttcag gatgcttcag
agagggcagc acttatacct ggtggtcttt ctgatggtca gttttattcc cctcctgaat
ccgaagcagg atctgaagaa gctgaagaaa aacaggacag tgagaaacca cttttagaac
tatgagtact acttttgtta aatgtgaaaa accetcacag aaagtcateg aggcaaaaag
aggcaggcag tggagtetee etgtegacag taaagttgaa atggtgaegt ecaetgetgg
ctttattgaa cagctaataa agatttattt attgtaatac ctcacagacg ttgtaccata
tecatgeaca titagitgee tgeetgigge tggtaaggta atgicatgat teatectete
ttcagtgaga ctgagcctga tgtgttaaca aataggtgaa gaaagtcttg tgctgtattc
ctaatcaaaa gacttaatat attgaagtaa cactttttta gtaagcaaga taccttttta
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tttaacactc tacatttccc ttgtttttta actcatgcac atgtgctctt tgtacagttt

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-10

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                              -20
                                                  ~ 15
ccc cct ctm wgc cgc gcc ttc gcc tgc cgc ggc tgt caa ctc gct ccg
                                                                      100
Pro Pro Leu Xaa Arg Ala Phe Ala Cys Arg Gly Cys Gln Leu Ala Pro
    -10
gag ege gge gee gag ege agg gat aca geg eee age ggg gte tea aga
                                                                      148
Glu Arg Gly Ala Glu Arg Arg Asp Thr Ala Pro Ser Gly Val Ser Arg
ttc tgc cct cca aga aag tct tgc cat gat tgg ata gga ccc cca gat
                                                                      196
Phe Cys Pro Pro Arg Lys Ser Cys His Asp Trp Ile Gly Pro Pro Asp
                                30
aaa tat toa aac ott oga oot gtt oac ttt tac ata oot gaa aat gaa
                                                                      244
Lys Tyr Ser Asn Leu Arg Pro Val His Phe Tyr Ile Pro Glu Asn Glu
                            45
tct cca ttg gaa caa aag ctt aga aaa tta aga caa gaa aca caa gaa
                                                                      292
Ser Pro Leu Glu Gln Lys Leu Arg Lys Leu Arg Gln Glu Thr Gln Glu
                        60
tgg aat caa cag ttc tgg gca aac cag aat ttg act ttt agt aag gaa
                                                                      340
Trp Asn Gln Gln Phe Trp Ala Asn Gln Asn Leu Thr Phe Ser Lys Glu
                   75
aaa gaa gaa ttt att cac tca aga cta aaa act aaa qqc ctq qqc ctq
                                                                      388
Lys Glu Glu Phe Ile His Ser Arg Leu Lys Thr Lys Gly Leu Gly Leu
               90
                                   95
aga act gaa toa ggt cag aaa gca aca ttg aat gca gaa gaa atg gcg
                                                                      436
Arg Thr Glu Ser Gly Gln Lys Ala Thr Leu Asn Ala Glu Glu Met Ala
           105
                                110
gac ttc tac aag gaa ttt tta agt aaa aat ttt cag aag cac atg tat
                                                                      484
Asp Phe Tyr Lys Glu Phe Leu Ser Lys Asn Phe Gln Lys His Met Tyr
        120
                           125
tat aac aga gat tgg tac aag cgc aat ttt gcc atc acc ttc ttc atg
                                                                      532
Tyr Asn Arg Asp Trp Tyr Lys Arg Asn Phe Ala Ile Thr Phe Phe Met
                       140
gga aaa gtg gcc ctg gaa agg att tgg aac aag ctt aaa caq aaa caa
                                                                      580
Gly Lys Val Ala Leu Glu Arg Ile Trp Asn Lys Leu Lys Gln Lys Gln
                   155
                                       160
aag aag age aac taggagteca etetgaceca gecagagtec aggtttecae
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Lys Lys Arg Ser Asn
                170
aggaagcara tggagctcct ttcacagggg ctctgagaaa aactggagct gatctcaaga
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agccccacat cttcctaagg ggccccatgg cctgtttggg ggcagggtag gtcctggggc
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actgtgggcc gcctgcctgc gtgaaataaa gcccaagcac	tgatgtgggc tgggaaaaaa	tctaggccag aaaaaa	cttgttgtca	cgtacgtggt	815 851
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ctg cag gca gcc ctg ct Leu Gln Ala Ala Leu Le -5	u Cys Val A 1	sn Ala Ile 5	Ala Val Leu	His Glu 10	160
gag cga ttc ctc aag aa Glu Arg Phe Leu Lys As 15	c att ggc t n Ile Gly T	gg gga aca Trp Gly Thr 20	gac cag gga Asp Gln Gly	att ggt Ile Gly 25	208
gga ttt gga gaa gag cc Gly Phe Gly Glu Glu Pro 30	o Gly Ile L	aa tca sag ys Ser Xaa : 5	sta atg avs Xaa Met Xaa 40	ctt att	256
cga tot gta aga acc gt Arg Ser Val Arg Thr Va 45	g atg aga g l Met Arg V 50	tg cca ttg al Pro Leu	ata ata gta Ile Ile Val 55	aac tca Asn Ser	304
att gca att gtg tta ct Ile Ala Ile Val Leu Le 60	t tta tta t u Leu Leu P 65	tt gga tgaa he Gly	twtcat tggag	gaaaat	354
ggakactcag aaraggacat g	gccaktaraa	kttattactt (	tggtcattat t	ggaatattt	414
atatettage tggetgaeet 1 tttetattta aaaaaaaaaa a	a	aaaaatgtaa a	agctgaaaat a	aaaccaggg	474 495
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<sup>&</sup>lt;211> 897

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<222> 862..867
<221> polyA site
<222> 886..897
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tgaggagctg gagctggtgg ggactgggcc gca atg gac aag ctg aag aag gtg
                                     Met Asp Lys Leu Lys Lys Val
                                      -55
ctg agc ggg cag gac acg gag gac cgg agc ggc ctg tcc gag gtt gtt
                                                                      162
Leu Ser Gly Gln Asp Thr Glu Asp Arg Ser Gly Leu Ser Glu Val Val
            -45
                             -40
                                                   -35
gag gca tct tca tta agc tgg agt acc agg ata aaa ggc ttc att gcg
                                                                      210
Glu Ala Ser Ser Leu Ser Trp Ser Thr Arg Ile Lys Gly Phe Ile Ala
        -30
                            -25
tgt ttt gct ata gga att ctc tgc tca ctg ctg ggt act gtt ctg ctg
                                                                      258
Cys Phe Ala Ile Gly Ile Leu Cys Ser Leu Leu Gly Thr Val Leu Leu
                        -10
                                           - 5
tgg gtg ccc agg aag gga cta cac ctc ttc gca gtg ttt tat acc ttt
                                                                      306
Trp Val Pro Arg Lys Gly Leu His Leu Phe Ala Val Phe Tyr Thr Phe
                                    10
ggt aat atc gca tca att ggg agt acc atc ttc ctc atg gga cca gtg
                                                                      354
Gly Asn Ile Ala Ser Ile Gly Ser Thr Ile Phe Leu Met Gly Pro Val
           20
                                25
aaa cag ctg aag cga atg ttt gag cct act cgt ttg att gca act atc
                                                                      402
Lys Gln Leu Lys Arg Met Phe Glu Pro Thr Arg Leu Ile Ala Thr Ile
       35
                           40
atg gtg ctg ttg tgt ttt gca ctt acc ctg tgt tct gcc ttt tgg tgg
                                                                      450
Met Val Leu Cys Phe Ala Leu Thr Leu Cys Ser Ala Phe Trp Trp
                        55
                                           60
cat aac aag gga ctt gca ctt atc ttc tgc att ttg cag tct ttg gca
                                                                      498
His Asn Lys Gly Leu Ala Leu Ile Phe Cys Ile Leu Gln Ser Leu Ala
                   70
                                       75
ttg acg tgg tac age ctt tcc ttc ata cca ttt gca agg gat gct gtg
                                                                      546
Leu Thr Trp Tyr Ser Leu Ser Phe Ile Pro Phe Ala Arg Asp Ala Val
               85
                                    90
aaa aad tgt ttt gcc gtg tgt ctt gca taattcatgg ccagttttat
                                                                     593
Lys Xaa Cys Phe Ala Val Cys Leu Ala
            100
gaagetttgg aaggeactat ggacagaage tggtggacag ttttgtwact atettegaaa
                                                                     653
cototgtott acagacatgt goottttatc ttgcagcaat gtgttgcttg tgattcgaac
                                                                     713
atttgagggt tacttttgga agcaacaata cattctcgaa cctgaatgtc agtagcacag
                                                                     773
gatgagaagt gggttctgta tcttgtggag tggaatcttc ctcatgtacc tgtttcctct
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aaaa
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                                                                  109
              Met Lys Ala Leu Cys Leu Leu Leu Pro Val Leu
ggg ctg ttg gtg tct agc aag acc ctg tgc tcc atg gaa gaa gcc atc
                                                                  157
Gly Leu Leu Val Ser Ser Lys Thr Leu Cys Ser Met Glu Glu Ala Ile
   - 5
                      1
                              5
aat gag agg atc cag gag gtc gcc ggc tcc cta ata ttt agg gca ata
                                                                  205
Asn Glu Arg Ile Gln Glu Val Ala Gly Ser Leu Ile Phe Arg Ala Ile
                                  20
age age att gge ega ggg age gag age gte ace tee agg ggg gae etg
                                                                  253
Ser Ser Ile Gly Arg Gly Ser Glu Ser Val Thr Ser Arg Gly Asp Leu
           30
                              35
                                                 40
                                                                  301
get act tgc ded ega ggd ttd gdd gtd acd ggd tgd act tgt ggd tdd
Ala Thr Cys Pro Arg Gly Phe Ala Val Thr Gly Cys Thr Cys Gly Ser
       45
ged tgt ggd teg tgg gat gtg ege ged gag acc aca tgt cac tgc dag
                                                                  349
Ala Cys Gly Ser Trp Asp Val Arg Ala Glu Thr Thr Cys His Cys Gln
  60
                      65
                                          70
                                                                  397
tge geg gge atg gae tgg ace gga geg ege tge tgt egt gtg eag eec
Cys Ala Gly Met Asp Trp Thr Gly Ala Arg Cys Cys Arg Val Gln Pro
                  80
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518
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<222> 111..155

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<222> 965..970

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<222> 986..996

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ttc ctg wgt cta atg acc ctg aca acc cat gtt cac tca agt gcc aag 164 Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val His Ser Ser Ala Lys - 5

cca aat gaa caa ccc tgg ttg ttg aac tagcacctaa ggtcttarat 211 Pro Asn Glu Gln Pro Trp Leu Leu Asn

271

ggtacgcgtt gctatacaga atctttggat atgtgcatca gtggtttatg ccaaattgtt

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331

ggctgcgatc accagctggg aagcaccgtc aaggaarata actgtggggt ctgcaacrga

natgggtcca cctgccggct ggtccgaggg cartataaat cccakctctc cgcaaccaaa torgatgata otqtqqttqc aattooctat ggaagtakac atattogoot tgtottaaaa 451 ggtcctgatc acttatatct ggaarccawa accctccagg ggactaawgg tgaaaacagt 511 ctcasctcca caggaacttt ccttgtggac aattctagtg tggacttcca gaawtttcca gacwdagaga tactgagaat ggctggacca ctcacagcag atttcattgt caawattcgt aacteggget cegetgacag tacagtecag kkeatettet ateaacecat catecacega tggagggara cggatttctt tccttgctca gcaacctgtg gaggaggtta tcagctgaca 751 teggetgagt getaegatet gaggageaac egtgtggttg etgaecaata etgteaetat 811 tacccagaga acatcaaacc caaacccaag cttcaggagt gcaacttgga tccttgtcca 871 qccaqqtcaq tcaaatttgc tagttcattt gtcataaaca taactcaagt tccaaatagg 931 991 ttatttaaat taaaatgaaa cgttttaatt aaaaataaaa tgaaattaaa catcaaaaaa 996 <210> 250 <211> 860 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 45..602 <221> sig peptide <222> 45..107 <223> Von Heijne matrix score 8.5 seq LLTIVGLILPTRG/QT <221> polyA\_signal <222> 828..833 <221> polyA site <222> 850..860 <400> 250 56 acctetetee aegaggetge eggettagga ecceeagete egae atg teg eee tet Met Ser Pro Ser -20 104 ggt ege etg tgt ett ete ace ate gtt gge etg att ete eee ace aga Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile Leu Pro Thr Arg -15 -10 gga cag acg ttq aaa gat acc acg tcc agt tct tca gca gac tca act 152 Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser Ser Ala Asp Ser Thr 1 5 10 atc atg gac att cag gtc ccg aca cga gcc cca gat gca gtc tac aca 200 Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp Ala Val Tyr Thr 20 25 248 gaa ctc cag ccc acc tct cca acc cca acc tgg cct gct gat gaa aca Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro Ala Asp Glu Thr 35 40 cca caa ccc cag acc cag acc cag caa ctg gaa gga acg gat ggg cct 296 Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly Thr Asp Gly Pro 55 344 cta gtg aca gat cca gag aca cac wak agc mcc aaa gca gct cat ccc Leu Val Thr Asp Pro Glu Thr His Xaa Ser Xaa Lys Ala Ala His Pro 75 65 70 act gat gac acc acg acg ctc tct gag aga cca tcc cca agc aca kac 392 Thr Asp Asp Thr Thr Leu Ser Glu Arg Pro Ser Pro Ser Thr Xaa

90

85

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atg acc cct tct tct atg atg aac aca ccc tcc gga aac sgg ggc tgt Met Thr Pro Ser Ser Met Met Asn Thr Pro Ser Gly Asn Xaa Gly Cys  115 120 125	488
tgg tcg cag ctg tgc tgt tca tca cag gca tca tca tcc tca cca gtg Trp Ser Gln Leu Cys Cys Ser Ser Gln Ala Ser Ser Ser Ser Pro Val	536
gca agt gca ggc agc tgt ccc ggt tat gcc gga atc att gca ggt gag Ala Ser Ala Gly Ser Cys Pro Gly Tyr Ala Gly Ile Ile Ala Gly Glu 145 150 155	584
tcc atc aga aac agg agc tgacaacctg ctgggcaccc gaagaccaag Ser Ile Arg Asn Arg Ser 160 165	632
cecectgeca geteacegtg eccageetee tgeateceet egaagageet ggeeagag ggaagacaca gatgatgaag etggageeag ggetgeeggt eegagtetee taceteee aaceetgeee geceetgaag getacetgge geettggggg etgteeetea agttatet tetgetaaga eaaaaagtaa ageaetgtgg tetttgeaaa aaaaaaaa	CC 752
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ctt ctc ccg ttg ctg ctg ctc tgc ggc cct tcc cag gat caa tgc Leu Leu Pro Leu Leu Leu Leu Cys Gly Pro Ser Gln Asp Gln Cys -15 -10 -5	101
cga cct gta ctc cag aat ctg ttg cag agc cca ggc ttg aca tgg agc Arg Pro Val Leu Gln Asn Leu Leu Gln Ser Pro Gly Leu Thr Trp Ser 1 5 10 15	149
ttg gaa gtg ccc act ggg aga gaa gga aag gaa ggt ggg gat cgg gga Leu Glu Val Pro Thr Gly Arg Glu Gly Lys Glu Gly Gly Asp Arg Gly	197
cca ggg cta akt ggg gcc act cca gcc agg agc cct cag ggc aag gag Pro Gly Leu Xaa Gly Ala Thr Pro Ala Arg Ser Pro Gln Gly Lys Glu 35 40 45	245
atg ggg aga caa agg acc aga aag gtg aag ggc cct gct tgg akt cac Met Gly Arg Gln Arg Thr Arg Lys Val Lys Gly Pro Ala Trp Xaa His 50 55 60	293

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aca gca aat cag gaa cta aac agg atg agg tot otg tot tot ggo too Thr Ala Asn Gln Glu Leu Asn Arg Met Arg Ser Leu Ser Ser Gly Ser	341
65 70 75 80 80 A 1 A 1 A 1 A 1 A 1 A 1 A 1 A 1 A 1 A	389
gtg cca gtg ggg cat ctg gag ggt ggc acg gtc aag ctt cag aag gac Val Pro Val Gly His Leu Glu Gly Gly Thr Val Lys Leu Gln Lys Asp	309
85 90 95	
acg ggc ctc cat tcc tgc ara gat ggt atg gct tct ctt gaa ggg acg	437
Thr Gly Leu His Ser Cys Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr	
100 105 110	
cca gct tca gtc ctg gct gat gct tgc cca gga ttc cat gat gtg aan	485
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115 120 125	533
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Pro Lys Leu Asn Arg Phe Leu Leu Leu Phe Ile Gly Phe Val Cys Val
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Thr Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg
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Ser	Glu	Leu	Glu	Asn	Arg	Glu	Leu	Leu	Glu	Gln	Xaa	Ala	Glu	Phe	Glu	
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-			Arg			_				,						
90					95											
		700	~~~~	.~~~		+-	200+	. + ~ !	- = ~ = ^	T200	atas	. = ~+·	- CC +	toot a	gatcac	753
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															ttatc	873
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-60
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Pro Gly Pro Tyr Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro
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Val Ala Pro Gln His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn
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aaaaaacttt atttttgttt ccagtacaga gcaaaacaac aacaaaaaaa cataactatg
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Val Ala Tyr Cys Met Thr Thr Arg Thr Tyr Tyr Thr Pro Thr Arg Met
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1

-10

- 5

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tcc ctg aac caa gag cca ttc gty tca aga gcc att cgt cca aag tac Ser Leu Asn Gln Glu Pro Phe Val Ser Arg Ala Ile Arg Pro Lys Tyr 40 45 50	422
tot ato aco tagocattgt akocatacoa agoogggott cotacttoco Ser Ile Thr 55	471
tetgetecce tegetect cetgeraart aaateteact gaccetegat geasetecaa geatatataa tatatata ataaaaccat abtetaaaaa atteaacca ggawaaataa asccaraaat tegtatgga aaaatetgea caaatttatt tegecageat ggttateatg getetattga attateett gaccetett aaagecaaag caaacgggat aaagtgatea actaettaee teteaataee aaaargaag cagaggeaa aateteeaw taatteata aaaacaatte teaketggge geggtggete weacetgtar teccaacaet tegggaggee saggtgggeg gateatgagg tegggagate aamaceatee teggetaacat ggtgaaacce catetetaet aaaattacaa aaaattrget ggggaggtg gegggaeet gtggteccag etacteggga ggetgaggea agagaatggt gtgaaccea ggggggeggag cetgcagtga getgagateg caccactgea etecageetg gggaacagtg agacteegte teaaaaaaaa aaah	531 591 651 711 771 831 891 951 1011 1071
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cgg ccc tgg tgg aag gtg ctg ccc ctc agc tgc ttc ctc gtg gcg ctg Arg Pro Trp Trp Lys Val Leu Pro Leu Ser Cys Phe Leu Val Ala Leu -20 -15 -10	344
atc atc tgg tgc tac ctg agg gag gag agc gag gcg gac cag tgg ttg  Ile Ile Trp Cys Tyr Leu Arg Glu Glu Ser Glu Ala Asp Gln Trp Leu  -5 1 5 10	392
aga cag gtg tgg qqa qaq gtq cca gaq ccc agt gat cqt tct gaq qaq	440

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Tyr Ser Glu Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln	402
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tot gao tao oga agt ato tgatotggtg toogtgaggg gacaogtatg	674
Ser Asp Tyr Arg Ser Ile	
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	114
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Met Ser Thr Trp Tyr Leu Ala Leu -80 -75  aat aag tcc tat aag aat aaa gac agc gtt agg att tat ctc agc ttg  Asn Lys Ser Tyr Lys Asn Lys Asp Ser Val Arg Ile Tyr Leu Ser Leu -70 -65 -60	
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Lys Ile Asn Asp Ala Thr Gln Glu Pro Val Asn Cys Thr Asn Tyr Thr
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Leu Xaa Xaa Cys Cys Cys Val Lys Asn Lys Thr Val Lys Asp Leu Lys	

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	15	20	)	25	
agt gaa ccc aa Ser Glu Pro As	sn Pro Leu Xa	a Xaa Met Me	g gac aac a et Asp Asn I	itc aga aaa cg :le Arg Lys Ar 40	gt 412 :g
30 gaa act gaa gt Glu Thr Glu Va 45	tg gtc taacac	35 cota taraaaa	atga acaaaat	= =	gc 467
tcaacctett etg tgactgaatg gtt tgtgtgtata sec	taaaacat ttct	agtara agggg	gaaaaa aaakt	taaac atgcact	attc 527 Egtt 587 639
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tcc tgg tgg tg Ser Trp Trp C					
ttt att aat a Phe Ile Asn I -10					
tat gcc tcg g Tyr Ala Ser G 5	gt act tat tt ly Thr Tyr Ph 10	c cta ata to e Leu Ile T	at atc agc a yr Ile Ser 1 15	aca gta acg co Thr Val Thr P: 20	ro s
agc tgg agg c Ser Trp Arg L			aatta gtggt:	aacag gtagatt	tgg 493
ttacctccca aa tttgaaagag ag gagcctcctg ct acagatgtgt tg ggacaacatg gc	gtgctggg attr aagtctcc ctgt ttcgcctc ctaa attttaaa gtgg	gttgcg cagg agtgct ggga gtatga ggcc	ctggtc tcag ttacag gcgt tgagcc ctgg	actect ggggte gageca cegeac	aagt 613 ccgg 673

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                                                                      120
atgtttcccg ggaagaactg ggataaaggg gtcccagcac c atg gag gac ccg aac
                                              Met Glu Asp Pro Asn
cct gaa gag aac atg aag cag cag gat tca ccc aag gag aga agt ccc
                                                                      224
Pro Glu Glu Asn Met Lys Gln Gln Asp Ser Pro Lys Glu Arg Ser Pro
cag ago coa gga ggo aac ato tgo cao otg ggg geo cog aag tgo acc
                                                                      272
Gln Ser Pro Gly Gly Asn Ile Cys His Leu Gly Ala Pro Lys Cys Thr
                                -50
                                                                      320
ege tge etc atc acc tte gea gat tec aag tte eag gag egt eac atg
Arg Cys Leu Ile Thr Phe Ala Asp Ser Lys Phe Gln Glu Arg His Met
                                                -30
                                                                      368
aag cgg gag cac cca gcg gac ttc gtg gcc cag aag ctg cag ggg gtc
Lys Arg Glu His Pro Ala Asp Phe Val Ala Gln Lys Leu Gln Gly Val
                        -20
                                            -15
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ctc ttc atc tgc ttc acc tgc gcc cgc tcc ttc ccc tcc tcc aaa gcc
Leu Phe Ile Cys Phe Thr Cys Ala Arg Ser Phe Pro Ser Ser Lys Ala
                                        7
                    - 5
                                                                      464
ckr rkc acc cac car egc agc cac ggt cca rec gec aag ccc acc etg
Xaa Xaa Thr His Gln Arg Ser His Gly Pro Xaa Ala Lys Pro Thr Leu
                                15
                                                                      512
ceg gtt gca acc act act gcc car ccc acc ttc cct tgt cct gac tgt
Pro Val Ala Thr Thr Thr Ala Gln Pro Thr Phe Pro Cys Pro Asp Cys
                                                3.5
                                                                      560
ggc aaa acc ttt ggg cag gct gtt tct ctg arg cgg cac csc caa atr
Gly Lys Thr Phe Gly Gln Ala Val Ser Leu Xaa Arg His Xaa Gln Xaa
                                            50
                        45
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cat dar dtc odt dcc oct oct ggc ace ttc gcc tgc aca rad tgc ggt
His Glu Val Arg Ala Pro Pro Gly Thr Phe Ala Cys Thr Xaa Cys Gly
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cag gac ttt gct car gaa rca ggg ctg cat caa cac tac att cgg cat
Gln Asp Phe Ala Gln Glu Xaa Gly Leu His Gln His Tyr Ile Arg His
                                    80
                                                                      711
gee egg ggg gga ete tgagtteage ttaageetet ceaeggtgae gggtggetet
Ala Arg Gly Gly Leu
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gtggctggta ggactcaccc atgatatggg gtgcaggaac tctggggggcc ctgaaggatt
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   Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp
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ttt cac aga aga tct ctg cca ggc aag gcc atc tta gag att gga gct
                                                                    155
Phe His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala
        -65 .
                           -60
gga gtg agc ctt cca gga att ttg gct gcc aaa tgt ggt gca gaa gta
                                                                    203
Gly Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val
                       -45
                                                                    251
ata ctg tca gac age tca gaa ctg cct cac tgt ctg gaa gtc tgt cgg
Ile Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg
                   -30 -25
-35
                                                                    299
caa agc tgc caa atg aat aac ctg cca cat ctg cag gtg gta gga cta
Gln Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu
                                   -10
                -15
aca tgg ggt cat ata tct tgg gat ctt ctg gct cta cca cca caa gat
                                                                    347
Thr Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp
                 5
            1
att atc ctt gca tct gat gtg ttc ttt gaa cca gaa rat ttt gaa gac
                                                                    395
Ile Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp
                      20
att ttg gct aca ata tat ttt ttg atg cac aar aat ccc aag gtc caa
                                                                    443
Ile Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln
                                      40
                   35
ttg tgg tct act tat caa gtt agg art gct gac tgg tca ctt gaa gct
                                                                    491
Leu Trp Ser Thr Tyr Gln Val Arg Xaa Ala Asp Trp Ser Leu Glu Ala
                                   55
tta ctc tac aaa tgg gat atg aaa tgt gtc cac att cct ctt gag tct
                                                                    539
Leu Leu Tyr Lys Trp Asp Met Lys Cys Val His Ile Pro Leu Glu Ser
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          65
 ttt gat gca gac aaa gaa rat ata gca gaa tct acc ctt cca gga aga
                                                                    587
Phe Asp Ala Asp Lys Glu Xaa Ile Ala Glu Ser Thr Leu Pro Gly Arg
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 cat aca gtt gaa atg ctg gtc att tcc ttt gca aag gac agt ctc
                                                                    632
His Thr Val Glu Met Leu Val Ile Ser Phe Ala Lys Asp Ser Leu
                       100
 tgaattatac ctacaacctg ttctgggaca gtatcaatac tgatgagcaa cctggcacac
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tgg aac cgt gtg aga atc cct aag gcg ggg aac cgc agc gca gtg aca Trp Asn Arg Val Arg Ile Pro Lys Ala Gly Asn Arg Ser Ala Val Thr -45 -40 -35	101
gtg cag aac ccc ggc gcg gcc ctt gac ctt tgc att gca gct gta att Val Gln Asn Pro Gly Ala Ala Leu Asp Leu Cys Ile Ala Ala Val Ile -30 -25 -20	149
aaa gaa tgc cat ctc gtc ata ctg tcg ctg aag agc caa acc tta gat Lys Glu Cys His Leu Val Ile Leu Ser Leu Lys Ser Gln Thr Leu Asp -15 -10	197
gca gaa aca gat gtg tta tgt gca gtc ctt tac agc aat cac aac aga Ala Glu Thr Asp Val Leu Cys Ala Val Leu Tyr Ser Asn His Asn Arg 1 5 10	245
atg ggc cgc cac aaa ccc cat ttg gcc ctc aaa cag gtt gag caa tgt Met Gly Arg His Lys Pro His Leu Ala Leu Lys Gln Val Glu Gln Cys 20 25 30	293
tta aag cgt ttg aaa aac atg aat ttg gag ggc tca att caa gac ctg Leu Lys Arg Leu Lys Asn Met Asn Leu Glu Gly Ser Ile Gln Asp Leu 35 40	341
ttt gag ttg ttt tct tcc aag taagtaagtg gtccarttgc tttgtgatgt Phe Glu Leu Phe Ser Ser Lys 50	392
ggtgggctgg gaactcaatg tottgtgatc kecettwgga ttketetakg etygekgttg	452
gaatataacc aattataccw cagctgtaka aatwttgttt taatgtgggg taccyggtgt	512
ktgtggtaat cttctgacat tgatctatgg gartgactgg tgtgacattg aaatctgggt	572
catggtagat tatattaaaa catcagtggg ctgttattgt gcttaactac ctcaagttga	632
gcttaaagca agtcttcact tgaaaactgc tatagaaatg ctttatattt aaaaatgaaa	692
gtaatgggar mttgcacata gctgaaaatg tgaagggtcg cccagggagg amatggaagc	752
totgtgotto ttotgocata cottgocota tgoatotott tgtttcaato otttgtcata tootttataa taaaotggta aatgtaaaaa aaaaaaa	812 849

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tee eec cag gee etg gag gae teg gge eeg gtg aat ate tea gte tea
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Ser Pro Gln Ala Leu Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser
        -95
                           -90
                                               -85
atc acc cta acc ctg gac cca ctg aaa ccc ttc gga ggg tat tcc cgc
                                                                     149
Ile Thr Leu Thr Leu Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg
                     -75
                                          -70
aac gtc acc cat ctg tac tca acc atc tta ggg cat cag att gga ctt
                                                                     197
Asn Val Thr His Leu Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu
                   -60
                                       -55 -50
tca ggc agg gaa gcc cac gag gag ata aac atc acc ttc acc ctg cct
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Ser Gly Arg Glu Ala His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro
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                                   -40
aca gcg tgg agc tca gat gac tgc gcc ctc cac ggt cac tgt gag cag
                                                                    293
Thr Ala Trp Ser Ser Asp Asp Cys Ala Leu His Gly His Cys Glu Gln
                               -25
                                                   -20
gtg gta ttc aca gcc tgc atg acc ctc acg gcc agc cct ggg gtg ttc
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Val Val Phe Thr Ala Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe
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ccg tca ctg tac agc cac cgc act gtg ttc ctg aca cgt aca gca acg
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Pro Ser Leu Tyr Ser His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr
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cca cgc tct ggt aca aga tct tca caa ctg cca gag atg cca aca caa
                                                                    437
Pro Arg Ser Gly Thr Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln
               20
                                   25
aat acg ccc aaa att aca atc ctt tct ggt gtt ata agg ggg cca ttg
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Asn Thr Pro Lys Ile Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu
                               40
gaa aag tot ato atg ott taaatoocaa gottacagtg attgttocag
                                                                    533
Glu Lys Ser Ile Met Leu
atgatgaccg ttcattaata aatttgcatc tcatgcacac cagttacttc ctctttgtga
                                                                    593
tggtgataac aatgttttgc tatgctgtta tcaagggcag acctagcaaa ttgcgtcaga
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gcaatcctga attitigtccc gagaaggtgg ctitiggctga agcctaattc cacagctcct
                                                                    713
tgttttttga gagagactga gagaaccata atccttgcct gctgaaccca gcctgggcct
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ggatgctctg tgaatacatt atcttgcgat gttgggttat tccagccaaa gacatttcaa
                                                                    833
gtgcctgtaa ctgatttgta catatttata aaaatctatt cagaaattgg tccaataatg
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cacgtgettt gecetgggta cagecagage cettcaacce cacettggae ttgaggaeet
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1073

1133

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caa agg cca gag tca cag gaa gga ctt ctt cca ggg aga tta gtg gtg
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Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val
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atg gag agg aga gtt aaa aat gac ctc atg tcc ttc ttg tcc acg gtt
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Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val
           15
                              20
ttg ttg agt ttt cac tct tct aat gca agg gtc tca cac tgt gaa cca
                                                                   192
Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro
                          35
ctt agg atg tgatcacttt caggtggcca ggaatgttga atgtctttgg
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Leu Arg Met
   45
ctcagttcat ttaaaaaaga tatctatttg aaagttctca rarttgtaca tatgtttcac
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                                                                   361
ggcattttct tggtagcaca aattttctta ttgcttaraa aattgtcctc cttgttattt
                                                                   421
ctgtttgtaa racttaagtg agttaggtct ttaaggaaag caacgctcct ctgaaatgct
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tgtctttttt ctgttgccga aatarctggt cctttttcgg gagttaratg tatarartgt
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                                                                     104
Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp Thr Arg Gln Leu Pro Leu
                        -20
                                           -15
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Leu Thr Ser Ala Leu His Gly Leu Gln Gln His Pro Ala Phe Ser
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Gly Val Ala Arg Leu Ala Lys Arg Trp Val Arg Ala Gln Leu Leu Gly
            10
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gag ggt ttc gct gat gag agc ctg gat ctg gtg gcc gct gcc ctt ttc
Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu Val Ala Ala Ala Leu Phe
                           30
ctg cac cct gag ccc ttc acc cct ccg agt tcc ccc cag gtt ggc ttc
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Leu His Pro Glu Pro Phe Thr Pro Pro Ser Ser Pro Gln Val Gly Phe
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                                                                     392
Leu Phe Val Asn Leu Asn Asn Glu Leu Thr Val Glu Glu Gln Val Glu
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Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser Val Trp Thr Gln Asp Gly
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ccc tca gcc car atc ctg cag cag ctt gtg gtc ctg gca gct gaa scc
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Pro Ser Ala Gln Ile Leu Gln Gln Leu Val Val Leu Ala Ala Glu Xaa
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Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp Pro Arg Gly Pro Gly Asp
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Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp Ile Tyr Asp Val Leu Ile
               155
                                   160
ege etg tet eet ege eat ate eeg egg eac ege eag get gtg gae ter
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Arg Leu Ser Pro Arg His Ile Pro Arg His Arg Gln Ala Val Asp Ser
           170
                              175
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Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu Ser Gln Pro Gly Pro Ser
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Ser	Leu	Met	Pro	Val	Leu	Gly	Xaa	Asp	Pro	Pro	Gln	Leu	Tyr	Leu	Thr	
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cag	CEC	arg	gag	gcc	ttt	999	gat	ctg	gcc	ctt	ttc	ttc	tat	gac	cag	824
215	пец	лаа	Glu	Ата	220	GIY	Asp	Leu	Ala		Phe	Phe	Tyr	Asp		
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His	Glv	Glv	gag Glu	Val	Tla	99°	y.c	Ctc	rgg	aag	CCC	acc	agc	ttc	cag	872
111.0	O-y	Oly	014	235	110	Сту	val	neu	240	туѕ	Pro	Thr	ser	245	GIn	
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Pro	Gln	Pro	Phe	Lys	Āla	Ser	Ser	Thr	Lvs	Glv	Ara	Met	Val	Met	Ser	320
			250	-				255	2	2	5		260		201	
cga	ggt	ggg	gag	cta	gta	atg	gtg	CCC	aat	gtt	gaa	gca	atc	ctg	gag	968
Arg	Gly	Gly	Glu	Leu	Val	Met	Val	Pro	Asn	Val	Glu	Ala	Ile	Leu	Glu	
		265					270					275				
gac	ttt	gct	gtg	ctg	ggt	gaa	ggc	ctg	gtg	cag	act	gtg	gag	gcc	cga	1016
Asp	Phe	Ala	Val	Leu	Gly		Gly	Leu	Val	Gln		Val	Glu	Ala	Arg	
3 C F	280	200	+ ~~	t		285					290					
Ser	Glu	Ara	tgg Trp	Thr	gra	tgat	ccca	igc t	ctgg	jagca	aa go	tgta	gaco	3		1064
295	Q1 u	9	111	TILL	300											
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ccca	ggag	at c	catc	cacc	t at	tago	cctg	ggc	ctgg	acc	tccc	taca	rat t	tccc	actcc	1364
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206

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Arg His His Ile Leu Gln Gln Phe Leu Val Arg Lys Ser Val Pro Leu

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20
gaa aat got toa ett eea tit eet eac etg gge agt tet etg tit aaa
                                                                      254
Glu Asn Ala Ser Leu Pro Phe Pro His Leu Gly Ser Ser Leu Phe Lys
                            35
att gtg ggc tgatttggtc ttcctctcct cctcccactg ttactgccct
                                                                      303
Ile Val Gly
    45
gcagcccttg ttcaggtgta cagaccctta ttctggcctc tagtgtcctt gtctgtcatg
                                                                      363
acacaccett cegeceaaat acetetgace ecaaggetgg aatggggetg gtaggarata
                                                                      423
agtttgctta ctcatartca tgtcctttct cttggcacct gcttccctgc ggtgtcctca
                                                                      483
aatggatttc tgtgtggcag tggartgatt gcatgaattt ttctgtaaca cattaacttt
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                                                                      603
aactggagcc caaakaaatt cccttagggc aagattatgt tataataraa aattgaattt
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cctgaggcag tggctgccac cccttttcar atgtttagtc ctgcaaatag catctttctt
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gtagtctgtg acatggatgg ggatgctagg gcccttaggg gcaaggggac taaactaaat
                                                                      783
caakttgagt ttttttccag caggggttar gggaggtact csctgttgat atttgacact
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                                                                     117
cca act ggc aag cag cta gct gac att ggc tat aag acc ttc tct acc
                                                                     165
Pro Thr Gly Lys Gln Leu Ala Asp Ile Gly Tyr Lys Thr Phe Ser Thr
               -25
                                    -20
tcc atg atg ctt ctc act gtg tat ggg ggg tac ctc tgc agt gtc cga
                                                                     213
Ser Met Met Leu Leu Thr Val Tyr Gly Gly Tyr Leu Cys Ser Val Arg
           -10
                              -5
gto tac cac tat tto cag tgg cgc agg gcc cag cgc cag gcc gca gaa
                                                                     261
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Val Tyr His Tyr Phe Gln Trp Arg Arg Ala Gln Arg Gln Ala Ala Glu

10 15	
gaa cag aag dac tca gga atc atg tagaactggg gggctte Glu Gln Lys Xaa Ser Gly Ile Met 20 25	ttc teetgagear 315
asakgcccaa ggcatgctgt ggagagactt cacctgccac cattto	cagg tcaacaggac 375
tagagogttg atggttttca aaccotgttg gaagaaagtg cocatg	gttt ctctggttct 435
gccartttga cagtttatgg argettttga ategtaatar caatgt	
cctacagaca ttaaataatt tgctgtgtca aaaaaaaaaa	536
The second of th	230
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TEED FIONO DUPICIES	
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Met Lys Lys Val Le	u Leu Leu Ile
-15	-10
aca gcc atc ttg gca gtg gct gtw ggt ttc cca gtc tc	t caa gac cag 161
Thr Ala Ile Leu Ala Val Ala Val Gly Phe Pro Val Se	r Gln Asp Gln
-5 1	5
gaa cga gaa aaa aga agt atc agt gac agc gat gaa tt	a get tea ggr 209
Glu Arg Glu Lys Arg Ser Ile Ser Asp Ser Asp Glu Le	u Ala Ser Glv
10 15 20	4
wit tit gig tic cot tac oca tat oca tit ogc coa ci	t cca cca att 257
Xaa Phe Val Phe Pro Tyr Pro Tyr Pro Phe Arg Pro Le	n Pro Pro Ile
25 30 35	4 110 110 110
cca ttt cca aga ttt cca tgg ttt aga cgt aat ttt cc	t att cca ata 305
Pro Phe Pro Arg Phe Pro Trp Phe Arg Arg Asn Phe Pro	The Deer The
• •	
10 50	55
oct gaa tot god oot aca act ood ott oot ago gaa aag	g taaacaaraa 354
Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Ly	5
60 65	
ggaaaagtca crataaacct ggtcacctga aattgaaatt gagcca	otto ottgaaraat 414
caaaattoot gttaataaaa raaaaacaaa tgtaattgaa atagca	caca gcatteteta 474
gtoaatatot ttagtgatot totttaataa acatgaaago aaaaaaa	aaaa aaacc 529

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aag aaa gtt ctc ctc ctg atc aca gcc atc ttg gca gtg gct gtt ggt
                                                                      107
Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val Gly
   -15
                       -10
ttc cca gtc tct caa gac cak gaa cga gaa aaa aga agt atc agt gac
                                                                      155
Phe Pro Val Ser Gln Asp Xaa Glu Arg Glu Lys Arg Ser Ile Ser Asp
                                   10
age gat gaa tta get tea ggg ttt ttt gtg tte eet tae eea tat eea
                                                                      203
Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr Pro
                               25
ttt cgc cca ctt cca cca att cca ttt cca aqa ttt cca tqq ttt aga
                                                                      251
Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe Arg
                           40
cgt aat ttt cct att cca ata cct gaa tct gcc cct aca act ccc ctt
                                                                      299
Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro Leu
                       55
ccg agc gaa aag taaacaagaa ggaaaagtca cgataaacct ggtcacctga
                                                                      351
Pro Ser Glu Lys
aattgaaatt gagccacttc cttgargaat caaaattcct qttaataaaa gaaaaacaaa
                                                                     411
tgtaattgaa atagcacaca qcattctcta qtcaatatct ttaqtqatct tctttaataa
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tgc agc tac gct acc agg aga tct cca agc gaa ctc agc ctc ctc cca Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser Glu Leu Ser Leu Leu Pro -20 -15 -10	161
age tee etg tgg gte eta gee aca age tet eea aca att act att gea Ser Ser Leu Trp Val Leu Ala Thr Ser Ser Pro Thr Ile Thr Ile Ala -5 1 5	209
ctc gcg atg gcc gcc ggg aat ctg tgc ccc ctt cca tca tkt cgt Leu Ala Met Ala Ala Gly Asn Leu Cys Pro Leu Pro Ser Ser Xaa Arg 10 15 20 25	257
crc aaa agg cgc tgg tgt cag gca asc car caa ara gct ctg ctg Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln Gln Xaa Ala Leu Leu 30 35 40	302
tagetgecae tgaaaaraag geggtgaete eageteetee eataaagagg tgggagetgt eeteggaeea geettacetg tgacaetgea eeteaegge eaceegaeta etttgeetee ttggatttee teeagggaga atgtgaeeta atttatgaea aataegtara geteaggtat eacttetagt tttaetttaa aaaataaaaa aatagagae	362 422 482 521
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aaacaggctg ctggcattga ggtctgctac aaaaanarta atg gtc cca tgg ccc Met Val Pro Trp Pro -55	175
agg ggc aag gtg aaa act gct cct att ccc atc tct agg ttt cct ttc Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile Ser Arg Phe Pro Phe -50 -45 -40	223
ctc cct acc cac gac cca ccc acc cca gca cat tgg tct cca gca tct Leu Pro Thr His Asp Pro Pro Thr Pro Ala His Trp Ser Pro Ala Ser -35 -30 -25 -20	271
Cat cag cag ttt aaa cat kkg tca ccc ctc ctc act ttg gcc ctg ctg His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu Thr Leu Ala Leu Leu -15 -10 -5	319
ggt cag tgc tct ctg ttc arc aat ttg agg aaa aaa ctt gca ggg caa Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys Lys Leu Ala Gly Gln 1 5 10	367
aaa gca aaa aaa tta cct tcc ttc tcc agc ctg ccc ctg aca ctc tgg	415

Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu Pro Leu Thr Leu Trp  15 20 25	
cca tta act cct caa ttt gct gag ctc act aca gtg gca caa aaa aaa Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr Val Ala Gln Lys Lys 30 35 40 45	463
ttg agg tgg tcc ggg acc cta ggt tgg ggt cca gtt ccc agc tgg gtt Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro Val Pro Ser Trp Val 50 55 60	511
caa ttt ttt tta ggg tgaatggagg garagttggg gactgaaaas ccttcaaara Gln Phe Phe Leu Gly 65	566
caatgttatt acagcaktet eccettatee aaakttteet titeetgadt titeagttage tatggteaac egettggaaa atakttgaac acagtacaat aaratattit gaggetggga ktggtggete atgeetgtaa taateecagg actitigtgar accaaktitig aaggateact tgaacceagg aktitigarac cascetggge aacatrgtra gaccteatet etacaaaaaa aaaaa	626 686 746 806 811
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ctt gtc cct gct cac ctc tct ggt ctc atc act tgc ctt ctt gca ttc Leu Val Pro Ala His Leu Ser Gly Leu Ile Thr Cys Leu Leu Ala Phe -20 -15 -10	281
tgg gtc cca gcc tcc tgt atc cag aga tgc agt ggc tct cca ttg cca Trp Val Pro Ala Ser Cys Ile Gln Arg Cys Ser Gly Ser Pro Leu Pro -5 1 5 10	329
ctc tgattcctcc tttcttttgg tcacagagaa agggtacttt ctctgtcaaa Leu	382
totcaactta gacttgactt cotccaagga gotttggota tactototo ewogaccocc accotggoat actacacara toactotggg ctcacttgco tgcctaatgg toatctcccc agtaaactgt aagotocttg agggcaagga ttgtgttgga atttttgtat taacagtgco tggcttggtg cotggcacct aaaaagcact caataaatgt ttgtttaatg aaaaaaaaa aaa	442 502 562 622 625

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                                                                       120
ttttgttctc tgctatgctc aggacccaga tcaaaggagc tcagtaacta tttacaggcg
                                                                       180
tacatcatat gtggaggaca cttatgctgt g atg gcc cca cac aca gct tcc
                                                                       232
                                    Met Ala Pro His Thr Ala Ser
                                        -35
ttt ggg gtc tgt ccc ctg ctc tcc gtt acc cgc gtg gta gcc act gag
                                                                       280
Phe Gly Val Cys Pro Leu Leu Ser Val Thr Arg Val Val Ala Thr Glu
                 -25
                                     -20
cac tgg ctc ttc ctg gct tca ctc tct ggc atc aaa act tat cag tcc
                                                                       328
His Trp Leu Phe Leu Ala Ser Leu Ser Gly Ile Lys Thr Tyr Gln Ser
            -10
                                 -5
tac atc tca gtc ttt tgc aag gtg aca ctt atc tgattaccta attcacacra
                                                                       381
Tyr Ile Ser Val Phe Cys Lys Val Thr Leu Ile
aggtgttaat ggtggtaatg gcataktatt tattacccca ggggacccak aacggtggta
                                                                       441
tcaaaacata tcattcccca gtggtttaaa actctggtag ctttccargg aatccaaagt
                                                                      501
ggaatccagt ctccttagct gawttcacag ggccccgtct gcacaacttg gcttctgtcg
                                                                      561
gettecetan ceetgaette ceaageetta gteateacce teteteceae ceagggetea
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<222> 801..812

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gct c Ala P	ro :	ctg Leu -60	agc Ser	tgc Cys	ctg Leu	tca Ser	ccg Pro -55	act Thr	aag Lys	tgg Trp	agc Ser	agt Ser -50	gtt Val	tct Ser	tcc Ser	106	
gca g Ala A	sp :	tca Ser	act Thr	gag Glu	aag Lys	tca Ser -40	gcc Ala	tct Ser	gcg Ala	gca Ala	ggc Gly -35	acc Thr	agg Arg	aat Asn	ctg Leu	154	
cct t Pro P -30	tt o	cag Gln	ttc Phe	tgt Cys	ctc Leu -25	cgg Arg	cag Gln	gct Ala	ttg Leu	agg Arg -20	atg Met	aag Lys	gct Ala	gcg Ala	ggc Gly ~15	202	
att c Ile L	tg a leu !	acc Thr	ctc Leu	att Ile -10	ggc Gly	tgc Cys	ctg Leu	gtc Val	aca Thr -5	ggc Gly	gtc Val	gag Glu	tcc Ser	aaa Lys 1	atc Ile	250	
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aat c Asn X	aa 2															346	
gag ag Glu Se 35	gc ( er (	ggc 3ly	tac Tyr	aac Asn	acc Thr 40	aca Thr	gcc Ala	car Gln	acg Thr	gtc Val 45	ctg Leu	gat Asp	gac Asp	ggc Gly	agc Ser 50	394	
atc ga Ile A	ac t sp 1	tay Tyr	ggc Gly	atc Ile 55	ttc Phe	caa Gln	atc Ile	aac Asn	agc Ser 60	ttc Phe	gcg Ala	tgg Trp	tgc Cys	aga Arg 65	cgc Arg	442	
gga aa Gly Ly	ag o ys I	ctg Leu	aag Lys 70	gag Glu	aac Asn	aac Asn	cac His	tgc Cys 75	cay His	gtc Val	gcc Ala	tgc Cys	tca Ser 80	gcc Ala	ttg Leu	490	
rtc ac Xaa Tl	hr A	gat Asp 35	gac Asp	ctc Leu	aca Thr	gat Asp	gca Ala 90	att Ile	atc Ile	tgt Cys	gcc Ala	arg Xaa 95	aaa Lys	att Ile	gtt Val	538	
aaa ga Lys Gl																586	
gag gg Glu Gl 115	gg a ly A	aga Arg	gac Asp	Leu	tcc Ser 120	gas Xaa	tgg Trp	aaa Lys	aaa Lys	ggc Gly 125	tgt	gag Glu	gtt Val	tcc Ser		631	
taaact	tqqa	a c	taaa	ccca	a aa	tact	ttac	asc	aaco		tago	att	ac a	ataa	atoto	691	
caaato	gcct	gt	gtca	tctt	g to	ccgt	ttcc	tac	caat	att	cctt	ctca	aa c	ttaa	agagg	751	
gaaaat	- ttaa	ig c	- tata	cttt	t aa	gaaa	ataa	ata	tttc	cat	ttaa	atgt	ca a	maaa	aaaaa	811	
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ctttcatttc attctagaag acccc atg caa gtt ccc cac cta agg gtc tgg
                                                                172
                         Met Gln Val Pro His Leu Arg Val Trp
                              -35
                                                                220
aca cag gtg awa gat acc ttc att ggt tat aga aat ttg gga ttt aca
Thr Gln Val Xaa Asp Thr Phe Ile Gly Tyr Arg Asn Leu Gly Phe Thr
                                          -15
                         -20
                                                                 268
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Ser Met Cys Ile Leu Phe His Cys Leu Leu Ser Phe Gln Val Phe Lys
                    -5
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ttttg atg gtg gcc ctg aac ctc att ctg gtt ccc tgc tgc gct gct tgg	170
Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp	
-10 -5	
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Cys Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser	210
5 10 15	
get get gat act ggg tet geg atg eag egt gag gee tgg get ggt	200
Ale his her the Civ Sor his Met Cir has her Civ his the his	266
Ala Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly 20 25 30	
tgg aga agg tca caa ccc ttc tct gtt ggt ctg cct tct gct gaa aga	314
Trp Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg	
35 40 45	
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Leu Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu	
55 60 65	
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Gly His Arg Ile Cys Asp Leu	
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assessed the transfer out and actions and actions as a second sec	653
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Ile Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser	100
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cca gtg cgt cca cct gta tcc acc tgg ggc cct agc tgg gcc cag ctc	200
Pro Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu	206
-10 var ing 110 var ber the trp Gry Pro Ser Trp Ala Gin Leu	

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gtc ttt tcc acc act ggc cca gcc ctg ctg ctg ctt ctg gtc agc ttc Val Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Leu Val Ser Phe 10 15 20	302
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gca aac ttc tca cca ggg gcc aga gtc agg ggg ccg gtg aag gtc ctg Ala Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu 40 45 50	398
gac agc agg agg ctc tac tcc tgc aaa tgg gta cag tct cag gac aac Asp Ser Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asn	446
tta gcc tcc agg aag cac tgc tgc tgc tgc tca tgg ggc tgg gcc cgc Leu Ala Ser Arg Lys His Cys Cys Cys Cys Ser Trp Gly Trp Ala Arg	494
70 75 80 85 tec tgaaaacetg tggcatgeec ttgwaceetg cttggcetgg ctttetgeet	547
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-10 -5 1	153
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20 25 30 35  caa gto tgc atc tcc aac gag gtg gtc gtc tct ttt agt gag tcy ccc	249
Gln Væl Cys Ile Ser Asn Glu Val Val Ser Phe Ser Glu Ser Pro	# I.

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cck gtg ggt ccd aaa gtg cct cct gct gtc tct ccc gcg ctg ggc tcg Pro Val Gly Pro Lys Val Pro Pro Ala Val Ser Pro Ala Leu Gly Ser 85 90	393
ggc gag cat ccs rva btg tgaatkkkga cttttttctc ckccatttga Gly Glu His Pro Xaa Xaa 100	441
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gc gcc acg acg cca gct cgc aac ctg agc tgc tac cag tgc ttc aag ys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln Cys Phe Lys 5 10 15	153
tc agc agc tgg acg gag tgc ccg ccc acc tgg tgc agc ccg ctg gac (al Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser Pro Leu Asp 0 25 30	201
29 30 33	
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tee egt gge tte eee etg ege ete eag gee ace gag gte egt ate tge Ser Arg Gly Phe Pro Leu Arg Leu Gln Ala Thr Glu Val Arg Ile Cys 5 10 15	154
cct gtg gaa ttc aac ccc aac ttc gtg gcg cgt atg ata cct aaa gtg Pro Val Glu Phe Asn Pro Asn Phe Val Ala Arg Met Ile Pro Lys Val 20 25 30 .	202
gag tgg tcg gcg ttc ctg gag gcg rmc gat aac ttg cgt ctg atc cag Glu Trp Ser Ala Phe Leu Glu Ala Xaa Asp Asn Leu Arg Leu Ile Gln 35 40 45 50	250
gtg ccg aga agg gcc ggt tgagggatat gaggagaatg aggagtttct Val Pro Arg Arg Ala Gly 55	298
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                                                                     100
Phe Leu Leu Arg Phe Phe Ile Phe Cys Ser Leu Asn Thr Leu Leu Leu
                           -10
ggt ggt gtt aat aaa att gcg gag aag ata tgt gga gac ctc aaa gat
                                                                     148
Gly Gly Val Asn Lys Ile Ala Glu Lys Ile Cys Gly Asp Leu Lys Asp
   1
         5
ccc tgc aaa ttg gac atg aat ttt gga agc tqc tat qaa qtt cac ttt
                                                                     196
Pro Cys Lys Leu Asp Met Asn Phe Gly Ser Cys Tyr Glu Val His Phe
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                                   25
aga tat ttc tac aac aga acc tcc aaa aga tgt gaa act ttt gtc ttc
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Arg Tyr Phe Tyr Asn Arg Thr Ser Lys Arg Cys Glu Thr Phe Val Phe
          35
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Ser Ser Cys Asn Gly Asn Leu Asn Asn Phe Lys Leu Lys Ile Glu Arg
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gaa gta kcc tgt gtt gca aaa tac aaa cca ccg agg tgagaggatg
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Glu Val Xaa Cys Val Ala Lys Tyr Lys Pro Pro Arg
                       70
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 aacacaaacg aaagaaaaga agaaagcaaa accaaaacca gcaccgatcc cgacatagat
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 cagtgacgtc tttttcttca g atg atc cta tgt ttc ctt ctt cct cat cat
                                                                      291
                         Met Ile Leu Cys Phe Leu Leu Pro His His
                         -15
                                             -10
cgt ctt cag gaa gcc aga cag att caa gta ttg aag atg ctt cca agg
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Arg Leu Gln Glu Ala Arg Gln Ile Gln Val Leu Lys Met Leu Pro Arg
                    1
                                     5
                                                         10
gaa aaa tta aga aga aga gaa gag aga aaa caa ata aat ggg aaa aaa
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Glu Lys Leu Arg Arg Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys
                                 20
raa agg aca aaa tat gaa aca cca aga aaa rga raa gga aaa aaa gga
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Xaa Arg Thr Lys Tyr Glu Thr Pro Arg Lys Xaa Xaa Gly Lys Lys Gly
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gga aac mac cmc wtw tkt cmc ctt tcc aar agg gac tgaaactggg
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Gly Asn Xaa Xaa Xaa Xaa Leu Ser Lys Arg Asp
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                                                                     109
               Met Ser Trp Thr Val Pro Val Val Arg Ala Ser Gln
                                              -25
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Arg Val Ser Ser Val Gly Ala Asn Xaa Leu Cys Leu Gly Met Ala Leu
    -20
                       -15
                                            -10
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Cys	ccg Pro	cgt Arg	caa Gln	gca Ala	Thr	cgc Arg	atc Ile	ccg Pro	ctc Leu 5	aac Asn	ggc Gly	acc Thr	tgg Trp	ctc Leu 10	ttc Phe	205
-5 acc Thr	ccc Pro	gtg Val	agc Ser	aag Lys	1 atg Met	gcg Ala	act Thr	gtg Val	aar	agt Ser	gag Glu	ctt Leu	att Ile	gag	cgt Arg	253
ttc Phe	act Thr	tcc Ser	15 gar Glu	aag Lvs	ccc Pro	gtt Val	cat His	20 cac His	agt Ser	aag Lys	gtc Val	tcc Ser	25 atc Ile	ata Ile	gga Gly	301
act	qqa	30 tcq	ata	qqc	atg	gcc	35 tgc	gct	atc	agc	atc	40 tta	tta	aaa	ggc	349
	45					50		Āla			55					397
Leu 60	agt Ser	gat Asp	gaa Glu	Leu	gcc Ala 65	Leu	Val	gat Asp	Leu	Asp 70	Glu	Xaa	Lys	Leu	Lys 75	
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aat Asn	att Ile	gtt Val	tgt Cys 95	agc	aaa Lys	rat Xaa	tac Tyr	ttt Phe 100	gtc	aca Thr	gca Ala	aac Asn	tcc Ser 105	aac Asn	cta Leu	493
Val	Ile	Ile 110	Thr	Ala	Gly	Ala	Arg 115	caa Gln	Xaa	Lys	Gly	Glu 120	Thr	Arg	Leu	541
aat Asn	tta Leu 125	stc Xaa	cag Gln	cga Arg	aat Asn	gtg Val 130	gcc Ala	atc Ile	ttc Phe	aag Lys	tta Leu 135	atg Met	att Ile	tcc Ser	agt Ser	589
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gtg Val	gat Asp	atc Ile	tta Leu	act Thr 160	tat Tyr	gta Val	gct Ala	tgg Trp	aag Lys 165	ttg Leu	agt Ser	gca Ala	ttt Phe	ccc Pro 170	aaa Lys	685
aac Asn	cgt Arg	att Ile	att Ile 175	qqa	agc Ser	ggc Gly	tgt Cys	aat Asn 180	ctg Leu	ata Ile	mhg Xaa	gct Ala	cgt Arg 185	ttt Phe	cgt Arg	733
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tgg Trp	atc Ile	ctc Leu	gga Gly	gag Glu	cat His	Gly	gac	tca Ser	agt Ser	gtt Val	cct Pro 215	gtg Val	tgg Trp	agt Ser	gga Gly	829
gtg Val 220	aac	ata	gct Ala	ggt Gly	gtc Val 225	cct	ttg	aag Lys	gat Asp	ctg Leu 230	aac	tct Ser	gat Asp	ata Ile	gga Gly 235	877
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gca Ala	act Thr	gcc Ala	tat Tyr 255	gag	att Ile	att Ile	aaa Lys	atg Met 260	aaa	ggt	tat Tyr	act Thr	tct Ser 265	tgg Trp	gcc Ala	973
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agg Arg	aga Arg 285	ata Ile	cat His	cca Pro	gtt Val	taa Ser 290	Thr	ata Ile	act Thr	aag Lys	ggc Gly 295	Leu	tat Tyr	gga Gly	ata Ile	1069
rat Xaa <b>3</b> 00	gaa	gaa Glu	gta Val	ttc Phe	ctc Leu 305	agt Ser	att	cct Pro	tgt Cys	atc Ile 310	ctg	gga	gag Glu	aac Asn	ggt Gly 315	1117
att	acc <b>T</b> hr	<b>a</b> ac Asn	ctt Leu	ata Ile	aag	ata	aag Lys	ctg Leu	acc Thr	cct	gaa Glu	gaa Glu	gag Glu	gcc Ala	cat	1165

320 325 330	
320 325 330 ctg aaa aga gca aaa aca ctc tgg gaa att cag aat aag ctt aag	1010
Leu Lys Lys Ser Ala Lys Thr Leu Trp Glu Ile Gln Asn Lys Leu Lys	1213
335 340 345	
	1266
Leu	
	1326
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Met Val Cys Leu Phe Phe Arg Leu Ile Phe Ser Glu His Leu Pro Ile	
-10 -5 1 5	
ata ggc act gtc act tct cac aaa act ggg aca cta act gtt tat cca	152
Ile Gly Thr Val Thr Ser His Lys Thr Gly Thr Leu Thr Val Tyr Pro	
10 15 20	
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Thr Ser Ala Gly	
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gctgcaggaa gtaagaaaga agaaaaaagg agtgataaag ataaaaaaaa	384
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aaaaaaaaa aaa	517

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-20 -15 -10  ctg tcc ccc tgt ctg acc gct cca aag tcc ccc cga ctt gct atg atg  Leu Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met  -5 1 5 10	325
-5 1 5 10  cet gac aac taaatateet tatecaaate aataaarwra raateeteee  Pro Asp Asn	374
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Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg

met fint pro fitte cys Leu Ala cys Leu Gly Arg Arg -25 -20 -15	
	78
Pro Leu Ala Ser Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser -10 -5	, ,
ggc agc cac tgg aca gag aga cca akt cag akt tca ccg tgg akt tct 33	26
Gly Ser His Trp Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser 5 10	
	77
Leu Ser Ala Thr Thr Arg Gly 20 25	
	37
	97
	57
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	77 37
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Pro Ala Arg Arg His Leu Leu Val Leu Leu Leu Leu Ser Thr Leu -20 -15 -10	
gtg atc ccc tcc gct gca gct cct atc cat gat gct gac gcc caa gag 20	) Q
Val Ile Pro Ser Ala Ala Ala Pro Ile His Asp Ala Asp Ala Gln Glu	, 9
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Ser Ser Leu Gly Leu Thr Gly Leu Gln Ser Leu Leu Gln Gly Phe Ser  15 20 25	
cga ctt ttc ctg aaa ggt aac ctg ctt cgg ggc ata gac agc tta ttc 30	)5

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														cac His		401
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gat Asp	ttg Leu	Lys	gth Val 110	ccc Pro	agg Arg	atg Met	gag Glu	gar Glu 115	aag Lys	gag Glu	gcc Ala	ctg Leu	gta Val 120	ccc Pro	mtc Xaa	<b>54</b> 5
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		atc					cgg							gcc Ala		641
	ggc					anc								gcc Ala		689
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				tcc					tcc					cac His		785
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Arg	Arg	Gln -40	aag Lys	Leu	Leu	Leu	Ala -35	Gln	Leu	His	His	Arg	Lys	Arg	Val	153
Lys	Ala -25	Ala	Gly aaa	Gln	Ile	Gln -20	Ala	Trp	Trp	Arg	Gly -15	Val	Leu	Val	Arg	201
Arg -10	Thr	Leu	ctg Leu	Val	Ala -5	Ala	Leu	Arg	Ala	Trp 1	Met	Ile	Gln	Cys 5	Trp	249
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tgc Cys	atc Ile 40	cgc Arg	atg Met	tgg Trp	cag Gln	tgc Cys 45	cgg Arg	caa Gln	tgt Cys	tac Tyr	cgc Arg 50	caa Gln	atg Met	tgc Cys	aat Asn	393
gct Ala 55	ctc Leu	tgc Cys	ttg Leu	ttc Phe	cag Gln 60	gtc Val	cca Pro	aaa Lys	agc Ser	agc Ser 65	ctt Leu	gcc Ala	ttc Phe	caa Gln	act Thr 70	441
Asp	Gly	Phe	tta Leu	Gln 75	Val	Gln	Tyr	Ala	Ile 80	Pro	Ser	Lys	Gln	Pro 85	Glu	489
ttc Phe	cac His	att Ile	gaa Glu 90	atc Ile	cta Leu	tca Ser	atc Ile	tgaa	aggo	ct g	gggg	catgg	ıa ga	acag	ıgctg	543
cact	acco	ta a	ıtaaa	tgtc.	t ga	.ccag	gtaa	aaa	aaaa	aaa						583

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gag Glu	gtc Val	cag Gln	aat Asn -40	cca	gat Asp	gtt Val	ctg Leu	tgg Trp -35	gat	ttg Leu	gac Asp	atc Ile	ccc Pro	gaa Glu	gcc Ala	273
agg Arg	agc Ser	cat His -25	gct	gac Asp	caa Gln	gac Asp	agc Ser -20	aac	ccc Pro	aag Lys	gcg Ala	gaa Glu -15	gcc Ala	ctg Leu	ctc Leu	321
ccc Pro	tgc Cys -10	aac	ctg Leu	cac His	tgc Cys	agc Ser -5	tgg Trp	ctc L <b>e</b> u	cac His	agc S <b>e</b> r	agc Ser 1	ccc Pro	agg Arg	cca Pro	gat Asp 5	369
ccc Pro	cat	tcc Ser	cac His	ttc Phe 10	cca Pro	tct Ser	ktc Xaa	agg Arg	agg Arg 15	tgc Cys	cct Pro	ttg Leu	ccc Pro	cac His 20	cct Pro	417
				ccc	ccs Pro		tgaa	accad	ctc 1	tgtct	taata	at co	cttt	ggcca	3.	468
gcti	caat ggaat	gy o	aagga caaga ggtga	cctti	tt co gt ag	cttca ggaaa	aaaa atgg	c tgi a aci	tagc taac	ctcc	tcto ggaa	cacto aggto	gaa ( ggt :	ggtg	accata ggagct acagag	528 588 648 697
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			Trp					ctc Leu	ttc				ttg	gtg	ttg Leu	222
		gat	gag				tgg	aac				ata			cca Pro 15	270
gtc Val	tgg	ata Ile	ttt Phe	gat Asp	act	atc Ile	ctt Leu	ctt Leu	gto Val	ctg	ctg Leu	att	gtg Val	aaa Lys	atg Met	318

823

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caagetttgg tgtatgtgtt ggeeggttet gaagtettga agaagetetg etgaggaaga
                                                                      120
ccaaagcagc actogttgcc aattagggaa tggaccgttt gggttccttt agca atg
                                                                      177
ate cet etg ata age cac ett gee gag get get eet eet ace tea teg
                                                                     225
Ile Pro Leu Ile Ser His Leu Ala Glu Ala Ala Pro Pro Thr Ser Trp
                                -25
            -30
ago ott ata toa agt gtg otg aat gtg ggo cao etc ett tit tee tet
                                                                     273
Ser Leu Ile Ser Ser Val Leu Asn Val Gly His Leu Leu Phe Ser Ser
                            -10
                                                - 5
get tge agt gtt tea etc gag get ttg agt aca aga aac atc aaa geg
                                                                     321
Ala Cys Ser Val Ser Leu Glu Ala Leu Ser Thr Arg Asn Ile Lys Ala
                                        10
atc ata ctt atg aaa taatggcttc agattttcct gtccttgatc ccagctggac
                                                                     376
Ile Ile Leu Met Lys
tgctcaagaa raaatggccc ttttagaasc tgtgatggac tgtggcttig gaaattggca
                                                                     436
ggatgtagcc aatcaaatgt gcaccaarac caaggaggag tgtgagaagc actatatgaa
                                                                     496
geattteate aataacceye tgtttgeate trsectgetg aacctgaaac aascagrgga
                                                                     556
agcaaaaact gotgacacag coattocatt toactotaca ratgaccoto cocgacokac
                                                                     616
ctttgactcc ttgctttctc gggacatggc cgggtacwtg ccmgctcgag cagatttcat
                                                                     676
tgaggaattt gacaattatg cagaatggga cttgagagac attgattttg ttgaagatga
                                                                     736
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<222> 191..304
<223> Von Heijne matrix
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      seq LAFLSCLAFLVLD/TQ
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<222> 766..771
<221> polyA site
<222> 804..817
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gagccatgag gggctgtggc agggagggc agggtgtgga aagactcccc tggggccatg
                                                                     120
gtggagatgt gctgaggtct tctccctgat cgtcttctcc tccctgctga ccgacggcta
                                                                     180
ccagaackag atg gag tot ccg cag ctc cac tgc att ctc aac agc aac
                                                                     229
          Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn
                       -35
age gtg gee tge age ttt gee gtg gga gee gge tte etg gee tte etc
                                                                     277
Ser Val Ala Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu
-25
                   -20
age tge etg gee tte etc gte etg gae aca eag gag ace ege att gee
                                                                     325
Ser Cys Leu Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala
               - 5
ggc acc ege tte aag aca gee tte cag ete etg gae tte ate etg get
                                                                     373
Gly Thr Arg Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala
                           15
gtt ctc tgg gca gtt gtc tgg ttc atg ggt ttc tgc ttc ctg gcc aac
                                                                     421
Val Leu Trp Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn
                       3.0
caa tgg cag cat tcg ccg ccc aaa gar kkc ctc ctg ggg agc agc agt
                                                                     469
Gln Trp Gln His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser
                                       50
                   4.5
gcc cag gca gcc atc ggc stt cac ctt ctt ctc cat cct tgt ctg gat
                                                                     517
Ala Gln Ala Ile Gly Xaa His Leu Leu Leu His Pro Cys Leu Asp
                                   65
               60
att cca rgc cta cct ggc akk cca gga cct ccg aaa tgatgctcca
                                                                     563
Ile Pro Xaa Leu Pro Gly Xaa Pro Gly Pro Pro Lys
gtcccttacm arcgcttcct ggatgaaggt ggcatggtgs kkaacaccct ccccttgccc
                                                                     623
totgocaaca gootgtgaac atgoccacca otggocccaa cagootgagt tatgotagot
                                                                     683
ctgccctgtc cccctgtctg accgctcmaa agtccccccg gcttgctatg atgcctgaca
                                                                     743
                                                                     803
actaaatate ettateeaaa teaataaaga gagaateete eeteeagaag ggtttetaaa
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aacaaaaaa aaaahncctt
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<210> 317

<211> 1112

<212> DNA

<213> Homo sapiens

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<222> 47..124
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<222> 1583..1588
<221> polyA site
<222> 1614..1623
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cag acg age ecc gte etg etg gee tee etg ggg gtg ggg etg gte act
Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly Leu Val Thr
                                -15
            -20
                                                                      151
ctg ctc ggc ctg gct gtg ggc tcc tac ttg gtt cgg agg tcc cgc cgg
Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg Ser Arg Arg
cet cag gte act ete etg gae ece aat gaa aag tae etg eta ega etg
                                                                      199
Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu Leu Arg Leu
                                        20
                   15
cta gac aag acg act gtg agc cac aac acc aag agg ttc cgc ttt gcc
                                                                      247
Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe Arg Phe Ala
                                    35
                                                                      295
ctg ccc acc gcc cac cac act ctg ggg ctg cct gtg ggc aaa cat atc
Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly Lys His Ile
                                 50
                                                                      343
tac ctc tcc acm mga att gat ggc agc ctg gtc atc agg cca tac act
Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg Pro Tyr Thr
                                                 70
                            65
                                                                      391
cot gto acc agt gat gag gat caa ggc tat gtg gat ctt gtc mtc aag
Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu Val Xaa Lys
                        80
                                                                      439
 gto tac otg aag ggt gtg cac ooc aaa ttt oot gag gga ggg aar atg
 Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly Gly Lys Met
                                         100
                    95
                                                                      487
 tot cak tac ctg gat asc ctg aaa gtt ggg gat btg gtg gaa ttt csg
 Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val Glu Phe Xaa
                                    115
                 110
                                                                      535
 ggg cca agc ggg ttg ctc act tac act gga aaa ggg cat ttt aac att
 Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His Phe Asn Ile
                                 130
                                                                      583
 cag ccc aac aag aat ctc cac cag aac ccc gag tgg cga aga aac tgg
 Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg Arg Asn Trp
                                                150
                            145
 gaa tgattgccgg cgggacagga atcaccccaa tgctacagct gatccgggcc
                                                                      636
                                                                      696
 atcctgaaag tccctgaaga tccaacccag tgctttctgc tttttgccaa ccagacagaa
 aaggatatca tettgeggga ggaettagag gaaetgeagg eeegetatee eaategettt
                                                                       816
 aagetetggt teactetgga teatececea aaagrttggg eetacageaa gggetttgtg
 actgeegaew tgateeggga acaeetgeee geteeagggg atgatgteet ggtaetgett
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tcacaaaaga tgcgattcac ctactgagca tcctccagct tccctggtgc tgttcgctgc
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agttgttccc catcagtact caagcactak aagccttagr ktcctktcct cagagtttca
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ggttttttca gttrsatcka gagctgaaat ctggatagta cctqcaggaa caatattcct
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gtagocatgg aagagggcca aggctcagtc actccttgga tggcctccta aatctccccg
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acctatgage aaatetgtat gtgtgagtat aagttgagea tageataett eeagaggtgg
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ngccctgtgt gatattgaaa aaaaaaa
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<222> 491..496
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                                                                      116
                                          Met Thr Pro Arg Ile Leu
ago gaa gto cag ttt toa goa ttt tgt cot tat tgg aca ata goa agg
                                                                      164
Ser Glu Val Gln Phe Ser Ala Phe Cys Pro Tyr Trp Thr Ile Ala Arg
            -55
                                -50
ata tha gaa ogt gtt ggt too gcg tgc the cgt cht gag tha tgt gct
                                                                      212
Ile Leu Glu Arg Val Gly Ser Ala Cys Phe Arg Leu Glu Leu Cys Ala
        -40
                            -35
                                                -30
gct att gtc gga tat ttt gtc tta gat gta cgt act ttc ctg ttc att
                                                                      260
Ala Ile Val Gly Tyr Phe Val Leu Asp Val Arg Thr Phe Leu Phe Ile
    -25
                        -20
gtg gta tgt gta att tgc gtt act ttg aat ttt cca cgt ttt tac ttt
                                                                      30B
Val Val Cys Val Ile Cys Val Thr Leu Asn Phe Pro Arg Phe Tyr Phe
-10
                    - 5
                                       1
ctt tgt ctc tca tca ctt acc gct ttt ggg acc ccc ccc atc ggg gtt
                                                                      356
Leu Cys Leu Ser Ser Leu Thr Ala Phe Gly Thr Pro Pro Ile Gly Val
           10
                                15
cac att ccc tct ccc tararcacac tcccttggat ttcctcradt ggggtctgct
                                                                      411
His Ile Pro Ser Pro
gcggtgaagc tttcccattt tatgtgcaga ttattttcag agggtatata gaattcaggc
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agctgtttcg ttgtagcaca ttaaaaaatat tttcccactt caaaaaaaaa aaacc
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Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Leu Kaa Leu Leu Leu
                                    -10
                -15
                                                                     151
cta ata gcc ttg gag atc atg gtt ggt ggt cac tct ctt tgc ttc aac
Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser Leu Cys Phe Asn
                                                                     199
ttc act ata aaa tca ttg tcc aga cct gga cag ccc tgg tgt gaa gcg
Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro Trp Cys Glu Ala
                        2.0
                                                                     247
cat gtc ttc ttg aat aaa aat ctt ttc ctt cag tac aac agt gac aac
His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr Asn Ser Asp Asn
                                        40
                   3.5
                                                                     295
aac atg gtc aaa cct ctg ggc ctc ctg ggg aag aag gta tat gcc acc
Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys Val Tyr Ala Thr
                                    55
               50
                                                                     343
ago act tgg gga gaa ttg acc caa acg ctg gga gaa gtg ggg cga gac
Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu Val Gly Arg Asp
                                70
            65
ctc agg atg ctc ctt tgt gac atc aaa ccc car ata aag acc agt gat
                                                                     391
Leu Arg Met Leu Cys Asp Ile Lys Pro Gln Ile Lys Thr Ser Asp
                            8.5
                                                                     439
cet tee act etg caa gte kar atk tit tgt caa egt gaa gea gaa egg
Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg Glu Ala Glu Arg
                        100
                                            105
                                                                      487
tgc act ggt gca tcc tgg cag ttc gcc acc aat gga gag aaa tcc ctc
Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly Glu Lys Ser Leu
                                       120
                    115
ctc ttt gac gca atg aac atg acc tgg aca gta att aat cat gaa gcc
                                                                      535
Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile Asn His Glu Ala
                                    135
                130
                                                                      583
agt wag atc aag gag aca tgg aag aaa gac aga ngg ctg gaa aak tat
Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa Leu Glu Xaa Tyr
                                                    155
                                150
           145
 ttc agg aag ctc tca aar gga gac tgc gat cac tgg ctc agg gaa ttc
                                                                      631
 Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp Leu Arg Glu Phe
        160
                           165
                                                                      679
 tta ggg cac tgg gaa gca atg cca raa ccg ama gtg tcm cca rta aat
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Leu Gly His Trp Glu Ala Met Pro Xaa Pro Xaa Val Ser Pro Xaa A	
175 180 185	sn
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	05
atc ctg ggg gca ttc atc ctg tta vtt tta atg gga att gtt ctc a	tc 775
Ile Leu Gly Ala Phe Ile Leu Leu Xaa Leu Met Gly Ile Val Leu I	le
210 215 220	
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Cys Val Trp Trp Gln Asn Gly Xaa Xaa Ser Thr Xaa Xaa	9 024
225 230	
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ac atg tgc cct agt ctg gaa gag gct ccc agt gtc aag ggg act ctg Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu	47
ac atg tgc cct agt ctg gaa gag gct ccc agt gtc aag ggg act ctg  Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu  -60  -55  -50	
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ac atg tgc cct agt ctg gaa gag gct ccc agt gtc aag ggg act ctg  Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu  -60  -55  ccc tgc tca gga caa cag cag cct ttc ccg ttt gga gcc tca aac at  Pro Cys Ser Gly Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Il	c 95
ac atg tgc cct agt ctg gaa gag gct ccc agt gtc aag ggg act ctg  Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu  -60  -55  ccc tgc tca gga caa cag cag cct ttc ccg ttt gga gcc tca aac at  Pro Cys Ser Gly Gln Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Il	c 95 e
ac atg tgc cct agt ctg gaa gag gct ccc agt gtc aag ggg act ctg  Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu  -60  -55  -50  ccc tgc tca gga caa cag cag cct ttc ccg ttt gga gcc tca aac at  Pro Cys Ser Gly Gln Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Il  -45  -40  -35  -3	c 95 e 0
ac atg tgc cct agt ctg gaa gag gct ccc agt gtc aag ggg act ctg  Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu  -60  -55  -50  ccc tgc tca gga caa cag cag cct ttc ccg ttt gga gcc tca aac at  Pro Cys Ser Gly Gln Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Il  -45  -40  -35  cca cta ctc ctg ggc agg agc aga aag gtg gct cga ggt gca ccg gtg	c 95 e 0 143
ac atg tgc cct agt ctg gaa gag gct ccc agt gtc aag ggg act ctg  Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu  -60 -55 -50  ccc tgc tca gga caa cag cag cct ttc ccg ttt gga gcc tca aac at  Pro Cys Ser Gly Gln Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn II  -45 -35 -3  cca cta ctc ctg ggc agg agc aga aag gtg gct cga ggt gca ccg gt  Pro Leu Leu Gly Arg Ser Arg Lys Val Ala Arg Gly Ala Pro Val	c 95 e 0 143
ac atg tgc cct agt ctg gaa gag gct ccc agt gtc aag ggg act ctg  Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu  -60 -55 -50  ccc tgc tca gga caa cag cag cct ttc ccg ttt gga gcc tca aac at  Pro Cys Ser Gly Gln Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn III  -45 -40 -35 -3  cca cta ctc ctg ggc agg agc aga aag gtg gct cga ggt gca ccg gtc  Pro Leu Leu Gly Arg Ser Arg Lys Val Ala Arg Gly Ala Pro Val  -25 -20 -15	c 95 e 0 c 143
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Glu Met Val Gln Ala Leu Tyr Glu Ala Pro Ala Tyr His Leu Ile Leu
                 -25
                                      -20
gaa ggg att ctg atc ctc tgg ata atc aga ctt ctt ttc tct aag act
                                                                   146
Glu Gly Ile Leu Ile Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr
               -10
                                   - 5
tac aaa tta caa gaa cga tct gat ctt aca gtc aag gaa aaa gaa gaa
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Tyr Lys Leu Gln Glu Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu
                                              15
                           10
ctg att gaa gag tgg caa cca gaa cct ctt gtt cct cct gtc cca aaa
                                                                   242
Leu Ile Glu Glu Trp Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys
                       25
gac cat cct gct ctc aac tac aac atc gtt tca ggc cct cca agc cac
                                                                   290
Asp His Pro Ala Leu Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His
                   40
                                       45
aaa act gtg gtg aat gga aaa gaa tgt ata aac ttc gcc tca ttt aat
                                                                   338
Lys Thr Val Val Asn Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn
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Phe Leu Gly Leu Leu Asp Asn Pro Arg Val Lys Ala Ala Ala Leu Ala
                               75
           70
                                                                   434
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Ser Leu Lys Lys Tyr Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr
                           90
                                                                   486
ggc aca ttt gaa tgaaratgaa ggatcattga tttccttgtg tatggataat
Gly Thr Phe Glu
    100
ccgggaacag gccaactaaa tatttgatga atgtatgatt tcaaatacag tgaattccct
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                                                                   786
grtgcctgtg gtcccagctr cgtgggaggc tgaggtggga gaattgcttc aacctgggag
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959
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844

904

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gaccettgga atgccaagtt caagtttage tatgtetege ggagaggeeg gtggaagaag
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aatttcccag cttctcctga agctcggtat ggccacaaca ctaaattctg cccgaggaga
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                                                                      354
                                 Met Phe Leu Lys Ser Gly Ala Gly
ett tet tea tge ett ett eet ett tge tgg etg gaa ege aaa gae eat
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Leu Ser Ser Cys Leu Leu Pro Leu Cys Trp Leu Glu Arg Lys Asp His
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ggc agg agg cca agc asc cat cct gga agg tgaaagcctc atactaagga
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 Gly Arg Arg Pro Ser Xaa His Pro Gly Arg
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cgtcaracag cgaaataara rectgggtee ttgaccetgt aaasatetee etecceatee
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             Met Val Val His Leu Leu Tyr Ala His Leu Ser Phe Thr
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                     -15
                                                                      752
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Ser Lys Arg Ala Val Val Met Leu Lys Leu Glu Ile Thr Phe
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59

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				tgt		tgc Cys			aca					drd		299
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aaaa	aaaa		aa													363
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atg Met -5	ctg Leu	tca Ser	agg Arg	gct Ala	gct Ala 1	ggt Gly	tgg Trp	tgc Cys	tgg Trp 5	tac Tyr	aag	gag Glu	ccc Pro	act Thr 10	cag Gln	160
cag Gln	ttt Phe	tct Ser	tac Tyr 15	ctt Leu	tgc Cys	ctg Leu	Pro	tgc Cys 20	ctt Leu	tca Ser	tgg Trp	Asn	aar Lys 25	aaa Lys	ggc Gly	208
aac Asn	gtt Val	ttg Leu 30	cag Gln	ctt Leu	cca Pro	aat Asn	ttc Phe 35	tgaa	raaa	ct a	atct	cara	t tg	gcag	ttaa	262
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cttt	ttat	tt t	taat	gtct	t ga	ctct	tcar	agt	tcgt.	acc	tcaa	aara	ac a	atga	raaca	382
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															ccctc	502
tarc	aatt	to t	acta	aaat	a to	caad	tara	ato	+++-	ctt.	ttac	aato	aa a	ttac	totat	562

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622

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<223> Von Heijne matrix

score 6.69999980926514 seg ILSTVTALTFARA/LD

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									_				_			
				- 5					1		~~~		5	222	act ·	296
tcc	att	tct	gag	ctc	tgc	aag	gga	caa	gaa	CLA	gag	Dro	car	999	V) a	270
ser	Ile		GIU	Leu	Cys	гÀг		Gill	GIU	ъеп	GIU	20	301	Оту	Α+ω	
	ctc	10					15		ata	200	ata		aaw	atc	tac	344
999	Leu	act	grg	gcc	Dra	Dro	Cla	900 2012	Val	Ser	Leu	Gln	Glv	Tle	Tvr	
GIY		IIII	vai	Ald	PIO	30	GIII	AIa	vai	DCI	35	0411	0-7		-1-	
	25 ctg	aat	+ ~~	ata	at a		ctt	+++	cac	tcc		acc	cta	raa	qna	392
acc	Leu	Dxo	mrr mrr	Tou	Tau	Cay	T.e.11	Dhe	His	Ser	Thr	Ala	Leu	Xaa	Xaa	
	пеп	PIO	пр	теп	45	GIII	шси	1110	1110	50					55	
40	cag		act	2 2 t		tot	cta	tct	cta		atc	t.ct	tca	tcc	cat	440
ULL	Gln	Cln	Dro	Acn	Glv	Ser	Len	Ser	Len	Asn	Tle	Ser	Ser	Ser	His	
лаа	GIII	GIII	FIO	60	Oxy	501	Doa		65			-		70		
act	ccr	rat	cca		acc	tac	acc	cta	gaa	cca	qqa	ata	gac	cct	acc	488
Δla	Pro	Xaa	Pro	Xaa	Thr	Cvs	Thr	Leu	Glu	Pro	Gly	Val	Asp	Pro	Thr	
ATO	110	1144	75	21.00		-7-		80					85			
caa	sct	atic		att	aat	ccc	cat	CCC	cca	сса	сса	atc	tta	aaa	abc	536
Arc	Xaa	Val	Cvs	Ile	Asn	Pro	His	Pro	Pro	Pro	Pro	Ile	Leu	Lys	Xaa	
711 3		90	-1-				95					100				
cct	ctg		ccc	tac	cct	aaa	ccc	caq	tta	ggt	acc	cat	gct	999	caa	584
Pro	Leu	Ser	Pro	Tvr	Pro	Lvs	Pro	Gln	Leu	Gly	Thr	His	Āla	Gly	Gln	
110	105			- 1 -		110				•	115					
ato	aat	taa	caat	tta	tgca	cagg	ta c	tagt	ttta	t tgi	tatt	accg	ttc	cagg	gta	640
-	Asn				-			_								
120																
		aaa	aaqt	atct	ca a	aaag	gcaa	c at	gggc	cgag	cgc	agtg	gct	cacg	cctgta	700
ato	ccaq	cac	tttq	qqaq	gc c	aagg	tggg	c ag	atcg	cctg	agg	tctg	gag	ttca	agacca	760
acc	taac	caa	cagg	qtqa	aa c	cccg	tctc	t ac	aaaa	atar	gaa	aatt	rgc	cagg	tgtggt	820
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ads	.tqcq	gag	gttg	cagt	ga g	ccga	gatt	g tg	ccac	tgcg	ctc	cagc	ctg	ggcg.	acagag	940
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	22 > 1															
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	S	eq V	VSFL	LLLA	GLIA	/TY										
	21> p			e												
<2:	22> 8	90	901													
		2 -														
	00> 3								~~~		~~-		-a	acta	aadadt	60
aag	gcago	ttc	cagg	atco	tg a	gato	cgga	ıy ca	9009 +~+	9990	~-~	2009	90L	dass	aagagt tgaaca	120
ta	ctgat	cta	tnna	tggc	ag a	gaaa	aaaa	ia ai	LgLg	acca	949	acyc	yca +a n	gcaa at d	tgaaca	171
ag	gaacr	cca	ca a	.cg r	wn n	mk t	icc a	ica 9	ac c	ore c	0 L L	0a 9	ہ اون	en O	aa aag lu Lys	4,1
			ľv			aa F	ne 1	nr A		65	CT D	CT A	aı A	- 11C	та шув 60	
					70			<b></b>			~+ ~	a+~	+~~			219
aa	g agg	ago	gag	cgg	gaa . C	yaa	agg	, cag	) adl	. alt	. 910 . 17-7	Tiers	- συυ - συν-	Arc	cag	
ьy	s Arc	Arg			i GIN	. G⊥U	ı Arg	-50			v a 1	ושע	-45	, 1119 :	Gln	
_ (1			~55			, <u>-</u>	. +++			r des	atc	· ~++			ttg:	267
CC	g ctc	י מננ	. acc	, rcc	, cag	, Lat		. ددد		yaa	. a.u		3,00		5	201

```
Pro Leu Ile Thr Leu Gln Tyr Phe Ser Leu Glu Ile Leu Val Ile Leu
             -35
aag gaa tgg acc tea aaa tta tgg cat egt caa age att gtg gtg tet
Lys Glu Trp Thr Ser Lys Leu Trp His Arg Gln Ser Ile Val Val Ser
                       -20
ttt tta ctg ctg ctt gct ggg ctt ata gct acg tat tat gtt gaa gga
                                                                    363
Phe Leu Leu Leu Ala Gly Leu Ile Ala Thr Tyr Tyr Val Glu Gly
                   -5
                                      1
gtg cat caa cag tat gtg caa cgt ata gag aaa cag ttt ctt ttg tat
Val His Gln Gln Tyr Val Gln Arg Ile Glu Lys Gln Phe Leu Leu Tyr
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gcc tac tgg ata ggc tta gga att ttg tct tct gtt ggg ctt gga aca
                                                                    459
Ala Tyr Trp Ile Gly Leu Gly Ile Leu Ser Ser Val Gly Leu Gly Thr
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                                              3.5
ggg ctg cac acc ttt ctg ctt tat ctg ggt cca cat ata gcc tca gtt
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Gly Leu His Thr Phe Leu Leu Tyr Leu Gly Pro His Ile Ala Ser Val
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aca tta gct gct tat gaa tgc aat tca gtt aat ttt ccc gaa cca ccc
                                                                    555
Thr Leu Ala Ala Tyr Glu Cys Asn Ser Val Asn Phe Pro Glu Pro Pro
                  60
                                      65
tat cct gat cag att att tgt cca gat gaa gag ggc act gaa gga acc
                                                                    603
Tyr Pro Asp Gln Ile Ile Cys Pro Asp Glu Glu Gly Thr Glu Gly Thr
                                   80
att tot ttg tgg agt atc atc tca aaa gtt agg att gaa gcc tgc atg
                                                                   651
Ile Ser Leu Trp Ser Ile Ile Ser Lys Val Arg Ile Glu Ala Cys Met
          90
                              95
tgg ggt atc ggt aca gca atc gga gag ctg cct cca tat ttc atg gcc
                                                                   699
Trp Gly Ile Gly Thr Ala Ile Gly Glu Leu Pro Pro Tyr Phe Met Ala
       105
                          110 . 115
aga gca gct cgc ctc tca ggt gct gaa cca gat gat gaa gag tat cag
                                                                   747
Arg Ala Ala Arg Leu Ser Gly Ala Glu Pro Asp Asp Glu Glu Tyr Gln
                      125
                                          130
gaa ttt gaa gag atg ctg gaa cat gca gag tct gca caa gta aga aca
                                                                   795
Glu Phe Glu Glu Met Leu Glu His Ala Glu Ser Ala Gln Val Arg Thr
                   140
                                      145
gtg ggg ata gaa aat aga aca ctt tac ttc cta aag agg cta tta
                                                                   843
Val Gly Ile Glu Asn Arg Thr Leu Tyr Phe Phe Leu Lys Arg Leu Leu
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                                  160
agg taaaattgtt agtagttact ctgaagaaga aaactgctaa agtaaaaaaa aaaaa
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Arg
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<sup>&</sup>lt;211> 1347

<sup>&</sup>lt;212> DNA

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

<sup>&</sup>lt;221> CDS

<sup>&</sup>lt;222> 138..671

<sup>&</sup>lt;221> sig\_peptide

<sup>&</sup>lt;222> 138..248

<sup>&</sup>lt;223> Von Heijne matrix score 3.5

seq LVFNFLLILTILT/IW

<sup>&</sup>lt;221> polyA\_signal

<sup>&</sup>lt;222> 1319..1324

<sup>&</sup>lt;221> polyA\_site

<222> 1338..1347

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aaya	atgu	ct t	, egaa	aaat	c tt	gata	aaat	ago	:cctt	atc	caqo	atttt	ta t	ctaa	aggaat	120
cago	апаа	ga c	rtaaa	iga a	ita d	aa a	ıga d	ag t	ca a	ag c	jtt a	itg t	ca g	gaa a	aag	170
CCCa	lagaa	94 0	3 5 5	,	iet (	ilu A	ira (	iln s	er A	arg V	al N	let S	er (	3lu I	Lys	
				•			.35			•		-30				
gat	αaα	tat	сад	ttt	caa	cat	cad	aaa	aça	ata	gag	ctg	ctt	gtc	ttc	218
) an	Glu	Tyr	Gln	Phe	Gln	His	Gln	Glv	Ala	Val	Glu	Leu	Leu	Val	Phe	
App	-25	- , -	0111		02	-20		2			-15					
aat	+++	tta	ctc	atc	ctt	acc	att	ttq	aca	atc	tgg	tta	ttt	aaa	aat	266
Agn	Phe	Leu	Leu	Ile	Leu	Thr	Ile	Leu	Thr	Ile	Trp	Leu	Phe	Lys	Asn	
-10	1110				-5					1				5		
cat	сда	ttc	cac	ttc	ttg	cat	gaa	act	gga	gga	gca	atg	gtg	tat	ggc	314
His	Arq	Phe	Arq	Phe	Leu	His	Glu	Thr	Gly	Gly	Ala	Met	Val	Tyr	Gly	
	5		10					15					20			
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Leu	Xaa	Met	Glv	Leu	Ile	Leu	Xaa	Tyr	Ala	Thr	Ala	Pro	Thr	Asp	Ile	
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Glu	Ser	Glv	Xaa	Val	Tyr	Asp	Cys	Val	Lys	Leu	Thr	Phe	Ser	Pro	Ser	
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act	cta	ctq	att	aat	atc	act	gac	caa	gtt	tat	gar	tat	aaa	tac	aar	458
Thr	Leu	Leu	Val	Asn	Ile	Thr	Asp	Gln	Val	Tyr	Glu	Tyr	Lys	Tyr	Lys	
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aga	qaa	ata	agt	caq	cac	amc	atc	aat	cct	cat	cam	gga	aat	gct	ata	506
Arq	Glu	Ile	Ser	Gln	His	Xaa	Ile	Asn	Pro	His	Xaa	Gly	Asn	Ala	Ile	
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Leu	Glu	Lys	Met	Thr	Phe	Asp	Pro	Xaa	Ile	Phe	Phe	Asn	Val	Leu	Leu	
			90					95					100			
cca	cca	att	ata	ttt	cat	gca	gga	tat	agt	cta	aag	aag	aga	cac	ttt	602
Pro	Pro	Ile	Ile	Phe	His	Ala	Gly	Tyr	ser	Leu	Lys	Lys	Arg	His	Phe	
		105					110					115				
ttt	caa	aac	tta	gga	tct	att	tta	acg	tat	gcc	ttc	ttg	gga	act	gcc	650
Phe	Gln	Asn	Leu	Gly	Ser	Ile	Leu	Thr	Tyr	Ala	Phe	Leu	Gly	Thr	Ala	
	120					125					130					
atc	tcc	tgc	atc	gtc	ata	999	taa	gtga	cat	tcgg.	agct	ca a	gttg	cagg	t	701
Ile	Ser	Cys	Ile	Val	Ile	Gly										• //*
135					140										,	5.63
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qaa	aatt	atc	tttt	tttt	ar t	awat	caca	w at	ttgt	atgt	ttt	ttcw	gac	ttaa	ttccac	821
ggc	ttck	gam	aaat	acaa	gg c	ttca	aatc	a aa	gcaa	acta	wag	gatt	gct	ggac	tttctc	881
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aca	qaqt	tgc	ttaa	taca	gg g	atag	cttt	t ca	gtta	atac	cct	gtag	aat	gcag	actett	1181
ttt	ttca	tta	tatt	ttct	tq a	ttat	gcta	c tg	agcc	ctaa	gtc	acac	gtt	atat	actetg	1241
gct	tgca	gct	catc	ataa	ag t	aaaa	tgtg	g ta	ccaa	atgg	tga	aggc	aat	ccag	cctctg	1301
ata	atcc	cgt	ccaa	taca	tt a	aagc	tcca	c tg	cagg	aaaa	aaa	aaa				1347

<sup>&</sup>lt;210> 339

<sup>&</sup>lt;211> 987

<sup>&</sup>lt;212> DNA

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

<sup>&</sup>lt;221> CDS

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                                                                     120
caa atg agc atg caa ttc ttg ttt aag atg gtg gcc tta tgc tgt tgt
                                                                     168
    Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys
        -20
                            -15
ctc tgg aag atc tcc ggc tgt gag gaa gtc cct cta act tac aac ctg
                                                                     216
Leu Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu
ctc aag tgc ctc cta gat aaa gcg cac tgt gta ctc ctg aca cct tgt
                                                                     264
Leu Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys
                15
                                    20
ggt tac atc ttt tcc ttg atc agt cca gaa att ctc aaa ctc act tta
                                                                     312
Gly Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu
                                35
atc act ttg cav atc ctc tta ata ctc aaa aat cta cac tta ctg tgg
                                                                     360
Ile Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp
                           50
ctg aca gtt tca agc awa tgt gtt cat cgc agt agt gca aga aaa gaa
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Leu Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu
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aag tagaagaacc ctgcagagat ttgatggaac ccagcttcta ttcattaaaa
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Lys
75
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atgttttccc tggggtgtgc tgattgtcag gcatcagttc cctgtgccat tcattcccca
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acacagcatg catcagaaat tttatcaata aatgctttct ctctcaatgt tcaacctatg
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ctgtggcaaa gaatatctaa taagatactc tcagcatttt gcacacttaa actaagatgc
                                                                     761
tgaatgctgt attttacgga ataatcagcc acattaaatt tggagactca acaagcatgc
                                                                     821
tgtgaacatt caacattagg tttaaatttt atttttaaaa gttaataata aaaggatata
                                                                     881
tgttaagtat tatgaaaccc tgcatatact gtaataaaat ggtggatgtg aatggacaat
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<210> 340
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<sup>&</sup>lt;211> 748

<sup>&</sup>lt;212> DNA

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

<sup>&</sup>lt;221> CDS

<sup>&</sup>lt;222> 372..494

<sup>&</sup>lt;221> sig\_peptide

<sup>&</sup>lt;222> 372..443

<sup>&</sup>lt;223> Von Heijne matrix

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<210> 341 <211> 1106 <212> DNA <213> Homo sapiens <220> <221> CDS <222> 112..450 <221> sig\_peptide <222> 112..192 <223> Von Heijne matrix score 7.19999980926514 seq SLLFFLLLEGGXT/EQ <221> polyA\_signal <222> 1053..1058 <221> polyA site <222> 1095..1106

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Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu Arg Trp
       10
                                                2.0
cat cct tac ctg gaa cct tat ggg ttg gtt tac tgc gtg aac tgc atc
                                                                     309
His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn Cys Ile
                        30
                                          . 35
tgc tca gag aat ggg aat gtg ctt tgc agc cga gtc aga tgt cca aat
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Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys Pro Asn
40
                  45
                                        50
gtt cat tgc ctt tct cct gtg cat att cct cat ctg tgc tgc cct cgc
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Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys Pro Arg
               60
tgc cca gaa gac tcc tta ccc cca gtg aac aat rwg gtg acc agc
                                                                     450
Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr Ser
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                                                                     510
ctctttcaga atcggcaacc cmatcaatgc acccagtgca gctgttcgga rggaaacktg
                                                                     570
tattgtggtc tcaagacttg ccccaaatta acctgtgcct tcccagtctc tgttccarat
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tectgetgee gggtwtgeag argagatgga caactgteat gggaacmtte tgatggtgat
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                                                                     810
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aaacacaagc atggacaagt gtgtgtttcc aatggaaaga cctattctca tggcgagtcc
tggcacccaa acctccgggc atttggcatt gtggagtgtg tgctatgtac ttgtaatgtc
                                                                    990
accaagcaag agtgtaagaa aatccactgc cccaatcgat acccctgcaa gtatcctcaa
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ccc Pro	tgg Trp	cag Gln	gca Ala	gcc Ala 20	ctg Leu	ttc Phe	gag Glu	aag Lys	acg Thr 25	cgg Arg	cta Leu	ctc Leu	tgt Cys	999 Gly 30	gcg Ala	263
acg Thr	ctc Leu	atc Ile	gcc Ala 35	ccc	aga Arg	tgg Trp	ctc Leu	ctg Leu 40	aca Thr	gca Ala	gcc Ala	cac His	tgc Cys 45	ctc Leu	aag Lys	311
Pro	Arg	Tyr 50	ata Ile	Xaa	His	Leu	Gly 55	Gln	cac His	Asn	Leu	Gln 60	Lys	Glu	Glu	359
Gly	Cys 65	Glu	Gln	Thr	Arg	Thr 70	Ala	Thr	gag Glu	Ser	Phe 75	Pro	His	Pro	Gly	407
ttc Phe 80	aac Asn	aac Asn	agc Ser	ctc Leu	ccc Pro 85	aac Asn	aaa Lys	gac Asp	cam Xaa	mgc Xaa 90	aat Asn	gac Asp	atc Ile	atg Met	ctg Leu 95	455
gtg Val	aak Xaa	atg Met	gma Xaa	tcg Ser 100	cca Pro	gtc Val	tcc Ser	atc Ile	acc Thr 105	tgg Trp	gct Ala	gtg Val	cga Arg	ccc Pro 110	ctc Leu	503
acc Thr	ctc Leu	tcc Ser	tca Ser 115	cgc Arg	tgt Cys	gtc Val	act Thr	gct Ala 120	ggc Gly	acc Thr	agc Ser	tgc Cys	ctc Leu 125	att Ile	tcc Ser	551
ggc Gly	tgg Trp	ggc Gly 130	agc	acg Thr	tcc Ser	agc Ser	ccc Pro 135	cag Gln	tta Leu	cgc Arg	ctg Leu	cct Pro 140	cac His	acc Thr	ttg Leu	599
cga Arg	tgc Cys 145	gcc	aac Asn	atc Ile	acc Thr	atc Ile 150	att	gag Glu	cac His	cag Gln	aag Lys 155	tgt Cys	gag Glu	aac Asn	gcc Ala	647
tac Tyr 160	ccc	ggc Gly	aac Asn	atc Ile	aca Thr 165	gac	acc Thr	atg Met	gtg Val	tgt Cys	gcc Ala	agc Ser	gtg Val	cag Gln	gaa Glu 175	695
ggg	ggc Gly	aag Lys	gac Asp	tcc Ser 180	tgc	cag Gln	ggt Gly	gac Asp	tcc Ser 185	999	ggc Gly	cct Pro	ctg Leu	gtc Val 190	tgt Cys	743
aac Asn	cag Gln	tct Ser	ctt Leu 195	caa	ggc Gly	att Ile	atc Ile	tcc Ser 200	tgg Trp	ggc Gly	cag Gln	gat Asp	ccg Pro 205	tgt	gcg Ala	791
atc Ile	acc Thr	Arg	aag	cct Pro	ggt Gly	gtc Val	tac Tyr 215	acg	aaa Lys	gtc Val	tgc Cys	aaa Lys 220	tat	gtg Val	gac Asp	839
	Ile					Lys			taga	actg	gac (		ccac	ca		886
acc tca aaa	ctaa cttaa tatte kwca	gcc ata gtg	aaga atca actc	ccct acct tggg	ct a gg gg aa t	cgaa gttc gaca	catto gaaat acaco	t tti	tggg gtga gttt	cctc gacc gttc	tgg:	gact attc gttg	aca ( aaa tat	ggag: ttct; cccc	taagaa atgctg gccttg agcccc aaaaaa	946 1006 1066 1126 1186 1191

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99

147

195

243

291

339

387

435

1070

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gag gaa gat gcc cag gat atg gat gcc tat acc ctg gcc aag gcc tac

Glu Glu Asp Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr

Phe Asp Val Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys 80

aat gca aga aaa gcc tat ttt ctg tat atg tat tcc aga tat ctg gtg

Asn Ala Arg Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val

agg gcc att tta aaa tgt cat tct gcc ttt agt gaa aca tcc ata ttt

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85

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                                                                     112
                           Met Arg Glu Pro Gln Lys Arg Thr Ala
                                    - 90
aca atc gca aaa tyc rrg gcs tva gag ggc ctc cga gac ccc tat ggc
                                                                     160
Thr Ile Ala Lys Xaa Xaa Ala Xaa Glu Gly Leu Arg Asp Pro Tyr Gly
                               -75
            -80
                                                                     208
ege etc tgt ggt age gag eac eec ega aga eea eet gag egg eec gag
Arg Leu Cys Gly Ser Glu His Pro Arg Arg Pro Pro Glu Arg Pro Glu
                           -60
                                               -55
gaa gac ccg agc act cca gag gag gcc tct acc acc cct gaa gaa gcc
                                                                     256
Glu Asp Pro Ser Thr Pro Glu Glu Ala Ser Thr Thr Pro Glu Glu Ala
                        -45
                                                                     304
tog ago act goo caa goa caa aag oot toa gtg ooc ogg ago aat ttt
Ser Ser Thr Ala Gln Ala Gln Lys Pro Ser Val Pro Arg Ser Asn Phe
                   -30
                                        -25
                                                                     352
cag ggc acc aag aaa agt ctc ctg atg tct ata tta gcg ctc atc ttc
Gln Gly Thr Lys Lys Ser Leu Leu Met Ser Ile Leu Ala Leu Ile Phe
               - 15
                                    -10
atc atg ggc aac agc gcc aag gaa gct ctg gtc tgg aaa gtg ctg ggg
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Ile Met Gly Asn Ser Ala Lys Glu Ala Leu Val Trp Lys Val Leu Gly
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aag tta gga atg cag cct gga cgt cas cac agc atc ttt gga gat ccg
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Lys Leu Gly Met Gln Pro Gly Arg Xaa His Ser Ile Phe Gly Asp Pro
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aag aar atc gtc aca gaa ran ttt gtg cgc aga ggg tac ctg att tat
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Lys Lys Ile Val Thr Glu Xaa Phe Val Arg Arg Gly Tyr Leu Ile Tyr
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                                        40
ara ccg gtg ccc cgt abc agt ccg gtg gag tat gas ttc ttc tgg ggg
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Xaa Pro Val Pro Arg Xaa Ser Pro Val Glu Tyr Xaa Phe Phe Trp Gly
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ccc cga gca cac gtg gaa tcg agc ara ctg aaa stc wtg cat ttt gtg Pro Arg Ala His Val Glu Ser Ser Xaa Leu Lys Xaa Xaa His Phe Val 65 70 75	592
gca agg gtt cgt aac cga tgc tct aaa gac tgg cct tgt aat tat gac Ala Arg Val Arg Asn Arg Cys Ser Lys Asp Trp Pro Cys Asn Tyr Asp 80 85 90	640
tgg gat tcg gac gat gat gca gag gtt gag gct atc ctc aat tca ggt Trp Asp Ser Asp Asp Asp Ala Glu Val Glu Ala Ile Leu Asn Ser Gly 95 100 105	688
get arg ggt tat tee gee eet taagtarate tgaggeagae eettggggggt Ala Xaa Gly Tyr Ser Ala Pro 110 115	739
gtaaaagaga gtcacaggta ccccaaggag tagatgccag ggtcctaagt tgaaaatgmt gtcgattggg ggcgggggac actgtatttg atatttgtga tcagtgatca ttgttcaact	799 859
gcgaaataga gtgtttgctt ttgataatgg aaaattgtat tcgttttaaa attccgtttg	919
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Met Asn Val Gly Thr Ala His Xaa Xaa Val Asn Pro Asn Thr Arg	
-35 -30 -25 gtk atg aac agc cgt ggc atc tgg ctc tcc tac gtg ctg gcc atc ggt	155
Val Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly	
ctc ctc cac atc gtg ctg ctg agc atc ccg ttt gtk agt gtc cct gtc	203
Leu Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val -5 1 5	
gtc tgg acc ctc acc aac ctc att cac aac atg ggc atg tat atc ttc	251
Val Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe 10 20	
ctg cac acg gtg aag ggg aca ccc ttt gag acc ccg gac cag ggc aag	299
Leu His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys 25 30 35 40	
geg agg etg eta acc cae tgg tgageagatg gattatgggg tecagtteae	350
Ala Arg Leu Leu Thr His Trp 45	
ggeetetegg aakttettga ceateacace categtgetg taetteetea ceagetteta cactaaktae raccaaatee attitgtget caacacegtg teeetgatra gegtgettat	410 470
cactualities raceasacto acceptate caseactyry tocolystia gegratical	± / U

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coccaagotg coccagotoc acggaktocg gatttttgga atcaataakt actgaaaktg
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                                                                      590
chctgaaaac araaaraara rscctctgga cactgccara ratgggggtt gagcctctgg
                                                                      650
cctaatttcc cccctcgctt cccccagtag ccaacttgga gtagcttgta ytggggttgg
                                                                     710
ggtaggcccc etgggetetg acettttetg aattttttga tetttteett ttgetttttg
                                                                     770
aatararact ccatggagtt ggtcatggaa aaaaaaaaaa
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                                                                     120
aaatgatgtc catttgagcc ccaccacgga ggttatgtgg tcccaaaagg aatgatggcc
                                                                     180
aagcaattaa tttttcctcc tagttcttag cttgcttctg cattgattgg ctttacacaa
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ctggcattta gtctgcatta cacaaataga cactaattta tttggaacaa gcagcaaa
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atg aga act tta ttt ggt gca gtc agg gct cca ttt agt tcc ctc act
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Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr
        -25
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ctg ctt cta atc acc cct tct ccc agc cct ctt cta ttt gat aga ggt
                                                                     394
Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly
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                                    1
etg tee etc aga tea gea atg tet tageceetet cetetettee atteetteet
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Leu Ser Leu Arg Ser Ala Met Ser
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rrrggcacat gactgaagta cctcagctgc gcagcctgta accagttttt ttaatgtaaa
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ggggcttcag attaaaaaaa aaa
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agaag atg ctg ggg ttt ttt ttg ttt ttg tcc ttt gta tta atg tat gat
      Met Leu Gly Phe Phe Leu Phe Leu Ser Phe Val Leu Met Tyr Asp
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ggt ttg cgc ctt ttt ggc att ctt tca aca tgt cgt gta cat cac acc
Gly Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr
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                                        10
    1
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atg aat cag tto cta att gat ata tot ago ttt acc too cga gtt aaa
Met Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys
                                    25
                                                                      374
aaa aaa atc ttt tta ttt tat gcc ttc awa ggt tgc ycg ttt car agt
Lys Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser
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         Met Ala Met Trp Asn Arg Pro Xaa Xaa Leu Pro Gln Gln
                             -50
                                                                      158
cot cts sta got gag coc act goa gag ggg gag coa cac ctg coc acg
Pro Leu Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr
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ggc	cgg	gas	pyg	act	gag	gcc	aac	cgc	ttc	gcc	tat	gct Ala	gcc	ctc	tgt .	206
-25		лаа	Ada	1111	-20	Ala	ASII	Arg	PHE	-15	Tyr	Ala	Ala	ьеи	-10	
		tcc	cta	tcc		tta	ttt	cet	gaa		gaa	cac	adc	tac		254
Gly	Ile	Ser	Leu	Ser	Gln	Leu	Phe	Pro	Glu	Pro	Glu	His	Ser	Ser	Phe	234
•				-5					1				5		1110	
tgc	aca	gag	ttc	atg	gca	ggc	ctg	gtg	ckm	tgg	ctg	gag	ttg	tct	gaa	302
Cys	Thr	Glu	Phe	Met	Ala	Gly	Leu	Val	Xaa	Trp	Leu	Glu	Leu	Ser	Glu	
		10					15					20				
get	gtc	ttg	cca	acc	atg	act	gct	ttt	gcg	agc	ggc	ctg	gga	ggt	gaa	350
WIG	25	пеп	PIO	Thr	мет	Inr	АТа	Pne	Ala	Ser		Leu	Gly	Gly	Glu	
gga	-	vma	tat	att	tat		22+	+++	ac+	~~~	35	CCC	a = +	a++	~~~	3.00
Gly	Xaa	Xaa	Cvs	Val	Cvs	Ser	Asn	Phe	Thr	Glu	Glv	Pro	Hie	T.en	Glu	398
40			-2-		45	201		1110	1111	50	Ory	FIU	1112	пеа	55	
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Gly	Arg	Pro	Asp	Gly	Asp	His	Ser	Gly	Pro	Ser	Glu	Leu	Leu	Thr	Gln	110
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Gly	Trp	Ala	Leu													
			75													
ctgo	ctcca	ag t	gccc	ttgg	ga gg	gaget	gga	gto	cctt	gaaa	agat	gtto	ct g	gaga	gcctg	558
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gga	cct.	cto :	ata i	a+~ /	~+~	++-	-80	~-~				-75				
gga Gly	Pro	Len I	Met 1	Leu :	900 Val	Dhe	Thr	Leu	yıı Val	get .	atc ·	cta (	CCC C	cat (	999 31	98
-	-70			u		-65	~ 11T	utu	val.		тте. -60	ыeu .	Jeu 1	ITS (	этү	
atg		acg 1	tat (	gac a			atc	caa	gao .			ata :	ata a	ממר :	aca	146
Met :	Lys '	Thr S	Ser A	Asp :	Thr	Ile	Ile	Arq	Glu :	Glv '	Thr	Leu M	rus : Met (	alv '	Thr	740
-55					-50					-45					-40	
gcc :	att 9	ggc a	acc t	igc t	tto :	ggc	tac	t <b>g</b> g	ctg	gga (	gtc ·	tca t	ca t	tc a	att	194
Ala :	Ile	3ly 7	Thr (	Cys 1	Phe (	Gly '	Tyr	Trp	Leu	Gly i	Val :	Ser S	Ser E	he :	Ile	
				D F												
tac ·				- 35					-30					-25		

=			Ala -20					-15					-10				
++a	aca	ata	cta	aac	tat	aac	ctc	ttt	ggg.	cat	tgc	att	gtc	ctg	ttc	25	90
Leg	y la	Leu	Leu	Glv	Tyr	Glv	Leu	Phe	Glv	His	Cys	Ile	Val	Leu	Phe		
пеα	AΙU	-5	псα	Cly	- 1 -	0-7	1		-		5						
- 4			aat			ctc		acc	ctc	ttc	tac	ct.c	ttc	taa	cta	3.3	38
atc	acc	m	Asn	#1-	TT	Tou	Ara	773	T.eu	Dhe	Tyr	Len	Phe	Trn	Leu		
	Thr	TAT	Asn	TIE		Tien	Arg	Ala	шси	20	- y -			1	25		
10					15				a + a		~~~	ata	tta	ata		3.8	36
ttg	gtg	ggt	gga	ctg	tcc	aca	ctg	cgc	alg	gra	yCa.	77.7	Tan	Val	Ser		
Leu	Val	GГУ	Gly		ser	Thr	ьeu	Arg	Mec	val	Ald	Val	пец	40	SCI		
				30					35					_	~~+	Δ.	34
cgg	acc	gtg	ggc	CCC	aca	cad	cgg	mtg	ctc	CTC	tgt	ggc	acc	č tg	31-	4.	J - I
Arg	Thr	Val	Gly	Pro	Thr	Xaa	Arg		Leu	Leu	Cys	GLY	Thr	ьеи	Ala		
			45					50					55			4.6	0.0
gcc	cta	cac	atg	ctc	ttc	ctg	ctc	tat	ctg	cat	ttt	gcc	tac	cac	aaa	4 (	82
Ala	Leu	His	Met	Leu	Phe	Leu	Leu	Tyr	Leu	His	Phe	Ala	Tyr	His	ьуs		
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Tle	Gln	Ara	Val	Pro	Arq	Asp	Ile	Pro	Ala	Met	Leu	Pro	Ala	Ala	Arg		
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Len	Dro	Thr	Thr	Val	Leu	Asn	Ala	Thr	Āla	Lvs	Ala	Val	Ala	Val	Thr		
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пец	GIII	261	125														
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WO 99/31236 -267- PCT/IB98/02122 -

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Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp Val Gly Ile Cys	
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J J J J J J J J J J J J J J J J J J J	1447
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cagattttgg ggaggcctta gtacggc atg atg agt tot gag ota cgg agg aac	234
Met Met Ser Ser Glu Leu Arg Arg Asn	
CCT Cat tto oto against the tto the training of the training	
Pro His Phe Ley Lys Ser Ash Ley Pho Ley Clar Ley Tel Car Wil	282
Pro His Phe Leu Lys Ser Asn Leu Phe Leu Gln Leu Val Ser His -20 -15 -10	
gaa att gtt tgc gct act gag act gtt act aca aac ttt tta aga cat	226
Glu Ile Val Cys Ala Thr Glu Thr Val Thr Thr Asn Phe Leu Arg His	330
I all the heart His	

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1 5 10	
gaa aag gog taatgaaaac catcoogtoo coattootoo tootototga	379
Glu Lys Ala	
15	
gggactggag ggaagccgtg cttctgagga acaactctaa ttagtacact tgtgtttgta	439
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cga gat ggc agc aaa att cgc aac ctg ctg ggg ttg gct ctg ggt cgg Arg Asp Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg	206
-20 -15 -10 ttg gag ggc ggc agt gct cgg cat gta gtg ttc tca ggt tct ggc agg	254

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Leu Glu Gly Gly Ser Ala Arg His Val Val Phe Ser Gly Ser Gly Ar	
got goa gga aag got gto ago tgo got gag att gto aag cog cgg gt	a 202 .
Ald Ala Gly Lys Ala Val Ser Cys Ala Glu Ile Val Lys Arg Arg Va 15 20 25	1
ccg ggc ctg cac cag ctc acc aag cta ckt ttc cft caa act gag co	c 350
Pro Gly Leu His Gln Leu Thr Lys Leu Xaa Phe Leu Gln Thr Glu As:	
age tgg gte dea see tea cet gae aca ggg eta rac dec ete aca gt Ser Trp Val Pro Xaa Ser Pro Asp Thr Gly Leu Xaa Pro Leu Thr Va	g 398
45 50 55	
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65 70	
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75 80 85 90	
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ryadayavat tot atg cat ggt tit gaa ata ata too tig aaa gag gaa	169
Met His Gly Phe Glu Ile Ile Ser Leu Lys Glu Glu -45	
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Ser Pro Leu Gly Lys Val Ser Gln Gly Pro Leu Phe Asn Val Thr Ser  -35  -20	
ggo toa toa toa coa gtg aco tog ttg ggo ota ctg tog ttg	265
-15 Leu Gly Leu Leu Ser Phe Gln Asn	•
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Leu His Cys P	he Pro Asp		Thr Glu Met		Ala Lys	
Gly Xaa Asn T	ct tgagccta	5 agg gtggg	gotada adaa	10 aaratt ctaatt	tacc <sup>.</sup>	365
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542

aat arg ggt ggt gat aga aag gtt gaa raa raa atg aar aag cac gga Asn Xaa Gly Gly Asp Arg Lys Val Glu Xaa Xaa Met Lys Lys His Gly 90 95 100	542
agt wet cat atg gga tte eea raa aac etg met aac ggt gee act get Ser Xaa His Met Gly Phe Pro Xaa Asn Leu Xaa Asn Gly Ala Thr Ala	590
gac aat ggt gat gga tta att ccm cca rgg aaa asc ara aca cct Asp Asn Gly Asp Asp Gly Leu Ile Pro Pro Xaa Lys Xaa Xaa Thr Pro	638
125 130 135  gaa agc cas caa ttt cct gac act gag aat gaa cag tat cac agg gac Glu Ser Xaa Gln Phe Pro Asp Thr Glu Asn Glu Gln Tyr His Arg Asp	686
140 145 150 ttt tct ggc cat ccc mac ttt ccc acd acc ctt ccc atc aaa cag Phe Ser Gly His Pro Xaa Phe Pro Thr Thr Leu Pro Ile Lys Gln	731
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ctc agt atc ttg gta gtg gct ggg tcc ggt ggg cat acc act gag atc Leu Ser Ile Leu Val Val Ala Gly Ser Gly Gly His Thr Thr Glu Ile	201
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70					75					80					85		
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Tyr	lle	His	Arg	Ile	Pro	Xaa	Ser	Arg	Glu	Val	Gln	Gln	Ser	Trp	Pro		
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Ser	Thr	Val		Thr	Thr	Leu	His		Met	Trp	Leu	Ser		Pro	Leu		
			105					110					115				
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Ile	His		Val	Lys	Pro	Xaa		Val	Leu	Cys	Asn		Pro	Gly	Thr		
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Cys		Pro	Ile	Cys	Val		Ala	Leu	Leu	Leu		Ile	Leu	Gly	lle		
	135					140					145					_	
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-	Lys	Val	Ile	Ile		Tyr	Val	Glu	Ser		Cys	Arg	Val	Lys			
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Leu	Ser	Met	Ser	-	Lys	lle	Leu	Phe		Leu	Ser	Asn	Tyr	Phe	TIE		
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Val	Gln	Trp		Ala	Leu	Ьуs	Glu		Tyr	Pro	гàг	ser		Tyr	Leu		
			185					190					195			-	2.2
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Gly	Arg		Val														
		200														7	93
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60 120 170

-15 -10 -5

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Thr	Leu	Tyr 15	Tyr	Гуs	t tg Leu	Ala	Val 20	Glu	Gln	Leu	Gln	Xaa 25	cat His	Pro	Glu	266
Ala	30	Glu	Ala	Leu	ggc Gly	Pro 35	Pro	Leu	Asn	Ile	His 40	Tyr	Leu	Lys	Leu	314
45	Asp	Arg	Glu	Asn	ttc Phe 50	Val	Asp	Ile	Val	Xaa 55	Ala	Lys	Leu	Lys	Ile	362
Pro	val	ser	Gly	Ser 65	aaa Lys	Ser	Glu	Gly	Leu 70	Leu	Tyr	Val	His	Ser 75	Ser	410
Arg	GIY	GIY.	Pro 80	Phe	cag Gln	Arg	Trp	His 85	Leu	Asp	Glu	Val	Phe	Leu	Glu	458
ьеп	ьуs	Asp 95	Gly	Gln	cag Gln	Ile	Pro 100	Val	Phe	Lys	Leu	Ser 105	Gly	Glu	Asn	506
GIY	Asp 110	Glu	Val	Lys		Glu 115										557
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tgaa	taca	aa a	gaaa	ctcc	t ot	aact toto	rggg	cac	aacg	aat	gcta	tttg	tc a	tttt	taaac	
tgta	taaa	aa a	gcac	atga	t aa	aagg	aatt	aga	gata stts	atg =+5	taat	gtat	tt g	aaag	tgctt tttaa	797
aaaa	aaaa	aa h	<i></i>			~~ <u>_</u>	Lacc	ugu	acta	aca	aaal	gill	gt t	gate	tttaa	857 868
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10

Asn \	Val 1	Asp	cgg ( Arg (	Gly 20	Ala	Gly	Ser	Ile	Arg 25	GIU .	Ala	GIY	СТУ.	30 ·	FIIC	206
Gly 1	Lуs .	Arg	gag ( Glu ( 35	cag Gln	Ala	Glu	Glu	Glu 40	Arg	Tyr	Phe	Arg	A1a 45	GIII	ser	254
aca q Thr	Glu	caa Gln 50	ctg Leu	gca Ala	rct Xaa	ttg Leu	aaa Lys 55	aaa Lys	crc Xaa	cat His	gaa Glu	gaa Glu 60	gar Glu	atc Ile	gtt Val	302
His :	His 65	Arg	gaa Glu	Gly	Asp											350
taag	caga catq	tc a	tcaa ttgc caga	ccac	t to	tgtg	ıtaaa	a cat	ggtt	ctg	gttt	aact	taa t	attt	agaat gtctg	410 470 519
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cac His	acc Thr	ttc Phe	att Ile	gtc Val	ctg Leu	cac His	ctg Leu	gtc Val	ttg Leu	caa Gln	999 Gly -5	atg Met	gtt Val	tat Tyr	act Thr	159
gag Glu 1	tac	acc Thr	tgg Trp	gaa Glu 5	gta Val	ttt	ggc Gly	tac Tyr	tgt Cys 10	cag Gln	gag Glu	ctg Leu	gag Glu	ttg Leu 15	tcc Ser	207
t.t.a	cat	tac	ctt	ctt	ctg	CCC	tat	ctg	ctg	cta	ggt	gta	aac	ctg Leu	ttt Phe	255
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Phe	Phe	Thr	ctg Leu	Thr	Cys	Gly	Thr	Asn	Pro	Gly	Ile	11e 45	Thr	гÀг	Ala	/
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cca Pro 65	aaa	aac Asn	gtg Val	agg Arg	tgc Cys 70	tct	act Thr	tgt Cys	gat Asp	tta Leu 75	agg Arg	aaa Lys	cca Pro	gct Ala	cga Arg 80	399
tee	aas Xaa	cac His	tgc Cys	akt Xaa 85	ata	tgt Cys	aac Asr	tgg Trp	tgt Cys 90	gtg	cac His	cgt Arg	ttc Phe	rac Xaa 95	cat His	447

cac	tgt	gtt	tgg	gtg	aac	aac	tgc	atc	999	gcc	tgg	aac	atc	agg	tmc	4 95
His	Cys	Val	Trp	Val	Asn	Asn	Cys		Gly	Ala	Trp	Asn	Ile	Arg	Xaa	
			100					105					110			
			tac													543
Phe	Leu		Tyr	Val	Leu	Thr	Leu	Thr	Ala	Ser	Ala	Ala	Thr	Val	Ala	
		115					120					125				
att	gtg	agc	acc	act	ttt	ctg	gtc	cac	ttg	gtg	gtg	atg	tca	gat	tta	591
Ile	Val	Ser	Thr	Thr	Phe	Leu	Val	His	Leu	Val	Val	Met	Ser	Asp	Leu	
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tac	cag	gag	act	tac	atc	gat	gac	ctt	gga	cac	ctc	cat	gtt	atg	gac	639
	Gln	Glu	Thr	Tyr	Ile	Asp	Asp	Leu	Gly	His	Leu	His	Val	Met	Asp	
145					150					155					160	
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Thr	Val	Phe	Leu	Ile	Gln	Tyr	Leu	Phe	Leu	Thr	Phe	Pro	Arg	Ile	Val	
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ttc	atg	ctg	ggc	ttt	gtc	gtg	gtt	ctg	arc	ttc	ctc	ctg	ggt	ggc	tac	735
Phe	Met	Leu	Gly		Val	Val	Val	Leu	Xaa	Phe	Leu	Leu	Gly	Gly	Tyr	
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			gtc													783
Leu	Leu		Val	Leu	Tyr	Leu	Ala	Ala	Thr	Asn	Gln	Thr	Thr	Asn	Glu	
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tgg	tac	aga	rgt	gac	tgg	gcc	tgg	tgc	cag	cgt	tgt	CCC	ctt	gtg	gcc	831
Trp		Arg	Xaa	Asp	Trp		Trp	Cys	Gln	Arg	Cys	Pro	Leu	Val	Ala	
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tgg	cct	ccg	tca	gca	gar	CCC	caa	gtc	cac	cgg	aac	att	cac	tcc	cat	879
Trp	Pro	Pro	Ser	Ala		Pro	Gln	Val	His		Asn	Ile	His	Ser	His	
225					230					235					240	
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Gly	Leu	Arg	Xaa		Leu	Gln	Glu	Ile		Leu	Pro	Ala	Phe	Pro	Cys	
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His	Glu	Arg	Lys	Lys	Gln	Glu										
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<222> 69..236

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<221> polyA\_signal

<222> 419..424

<221> polyA\_site

<222> 441..452

<400> 360

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aga	tica	tac	age	aga	aqc	aga	aaa	agg	caa	acg	aga	aga	agg	agg	aac		158
Ara	Ser	Cvs	Ser	Ara	Ser	Arq	Lys	Arg	Gln	Thr	Arg	Arg	Arg	Arg	Asn		
лгу	5-1	-40		J			-35	_				-30					
~ ~ ~	aat	auc	+++	ata	act	tca	tat	cca	acc	ctc	ttg	CCC	ttc	gcc	tgt		206
Dra	cor	Car	Dhe	Val	Ala	Ser	Cvs	Pro	Thr	Leu	Leu	Pro	Phe	Ala	Cys		
PIO		per	FIIC	Val	Ala	-20	0,0				-15						
	-25	~~~	~~~	201	000		aca	ctc	aca	ttt	cat	cct	gta	ktg	ctc		254
gtg	CCT	gga	gcc	agı	200	mb-s	The	Lou	715	Phe	Dro	Pro	Val	Xaa	Leu		
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aca	ggt	ccc	avc	acc	gat	ggc	att	CCC	DL -	gcc	Lou	Van	Sar	Ala	Ala		
Thr	Gly	Pro	Xaa	Thr	Asp	GTA	шe	Pro	Pne	Āla	ьец	лаа	20	Aru	71.1.0		
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ggt	CCC	ttt	tgt	gct	tcc	ttc	CCC	tca	ggt	avc	CTC	ECT	Door	7000	999		550
Gly	Pro	Phe	Cys	Ala	Ser	Phe	Pro	Ser	GтУ	Xaa	ьеп	Ser	PIO	PIO	GIY		
		25					30					35					200
cca	ata	ccq	aaa	qtq	agg	qgg	tta	CCC	ctt	ccc	agt	gtt	ttt	tat	tcc		398
Dro	T.em	Pro	Glv	Val	Ara	Glv	Leu	Pro	Leu	Pro	Ser	Val	Phe	Tyr	Ser		
FIO	40	110	017	,	5	45					50						
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tgt	999	31-	Tia	Dro	Tuc	Val	T.011	Lvs	Val	Ala	Leu						
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\22						2651	4										
			MPV				_										
	2	eq 1	JI'IE V I	· LVT	Smenn	1, 00											
	_																
	21> p			.e													
<22	22> 8	364	. 875														
<40	00 > 3	361							. ~ '	بارد. <u>مدید</u> ر		+	7227	gaar	acct	.aa	60
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gaa	acco	gctt	tato	catco	ett g	gtgta	atgta	ac to	ggcag	gcatt	aag	JUUNG	,,,,,,,	acco	agaa	++	180
ctt	-aatt	caa	taad	ctidaa	aac a	acaqt	cgaa	aa ac	gaata	actgt	; gaa	actat	gca	ayu	acage		
ta	-+++	aca	ccaa	attta	att (	ctcca	agata	at qo	cctt	cacgg	g CE	ccaa	attc	aay	acaca	i C C	240
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aa	actt!	taca	taar	ttaad	gag 1	tati	ccto	ct ta	acago	catgt	: gag	gtati	cat	gee	Lucy		360
99	-~	2754	222	33: -=++	J-∋ '	taaci	tacti	ta a	tatta	ataaa	a gca	aatat	tgc	atca	atatt	at	420
99	age Co	~~L~	uad!		3-4 ·		aata!	 	gagto	aticat	at.	atta	ggaa	agc	cttac	tt	480
ta	LLCG	actg	alg		911 (		34 CY	u;  r+ +-	: :	aaa+	י אמן	-+++	ttaa	ata	aatgt	gg	540
ar	aara	tgtt	cat	ugga	act i	adld	acya!	A 0 -	- ~ ~ ~ ·	~33°	- ~5'	7222	- יישיי	kaa	aaaaa	itc	600
ga	aara	acac	agc	atac	aga i	atgg.	ctaa	ud a	uyadi	19 L L (	_ a u	Jaaa	3~g -	115U	aaaaa	188	654
aa	atca	aatc	ata	atta	gat .	atga	agt a	atg	cta :	rag (	CCC '	cca a	agg 9	ycc .	aca c	aua	00.1
							1	Met	Leu :	Xaa 1	Leu :	ser 2	arg A	нта ,	THT 1	ay s	
											-25					-20	200
ra	c aa	c ca	g ac	g ca	g ta	g ct	t at	g cc	t gt	a ato	C CC	a gc	a ct	t ca	g gag	3	702
Xa	a Gl	v Ar	g Al	a Ar	g Tr	p Le	u Me	t Pr	o Va	1 11	e Pr	o Al	a Le	u Gl	n Glı	1	
				- 1	5				- 1	0				- 5			
~~	a an	n ac	a dd			a ca	a aa	t ca	a aa	a tt	t qa	a ac	t ag	c ct	g gc	2	750
gc	c ya	90	~ 55	י שש		3	25		J J				_				

Ala Xaa Ala Gly Gly Ser Arg Gly Gln Glu Phe Glu Thr Ser Leu Ala	
1 5 10	
aac atg gag act gag gca gga gaa ttg ctt aaa ccc agg agg cgg agg Asn Met Glu Thr Glu Ala Gly Glu Leu Leu Lys Pro Arg Arg Arg Arg 15 20	798
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Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg	111
-10 -5 1 cgt cct tct atg gcc gct tca ggc act tct tgg ata tca tcg acc ctc	159
Arg Pro Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu	159
5 10 15	202
gca cac tot tig toa oig aga gao gto toa gag agg oig igo ago igo Ala His Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys	207
20 25 30	
tgg agg act ata agc atg gga ccc tgc gcc cgg ggg tca cca atg aac Trp Arg Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn	255
35 40 45	
age tet gga gtg cae aga aaa tea age agg eta tte tae ate egg aca Ser Ser Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr	303
50 55 60 65	
cca atg aga aga tot toa tgo cat tta gaa tgt org gtt ata tto ott Pro Met Arg Arg Ser Ser Cys His Leu Glu Cys Xaa Val Ile Phe Leu	351
70 75 80	
ttg gga cgc caa ttg taaktgttac cttcaaagga tttccttttc taaaaaatta Leu Gly Arg Gln Leu	406
85	
ttttaratgt ctaactttat gttattgctc acgggtattt gactgaattg ttgatttagg	466
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                                                                      111
          Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg
                                          - 5
                      -10
cgt cct tct atg gcc gct tca ggc act tct tgg ata tca tcg acc ctc
                                                                      159
Arg Pro Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu
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gca cac tot ttg toa otg aga gac gto toa gag agg otg tgc ago tgc
Ala His Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys
                                                 3.0
                            25
tgg agg act ata agc atg gga ccc tgc gcc cgg ggg tca cca atg aac
                                                                      255
Trp Arg Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn
                                             45
                        40
                                                                      303
age tet gga gtg cae aga aaa tea age agg eta tte tae ate egg aca
Ser Ser Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr
                    55
                                         60
cca atg aga aga tot toa tgc cat tta raa tgt cag gtt ata ttc ctt
                                                                      351
Pro Met Arg Arg Ser Ser Cys His Leu Xaa Cys Gln Val Ile Phe Leu
                                     75
                70
ttg gga cgc caa ttg tagtcggtct tctcttgccc aaccagacac tggcatccac
                                                                      406
Leu Gly Arg Gln Leu
            85
tgtcttctgg cagtggctga accagagcca caatgcctgt gtcaactatg caaaccgcaa
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tgcraccaag ccttcacctg catccaagtt catccaggga tacctgggag ctgtcatcag
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cgccgtctcc attgctgtgg gccttatktc ctggttcaga aagccaacaa gttcacccca
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gecaccegee tteteateca gaggtttgtg cegtteeetg etgtagecag tgccaatate
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gatggcaacc tcgtgggctc ctccaagatc gcagcccgac acgccctgct ggagacggcg
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tragagatty aaacatroca attagagery gagatagere aggeracyay cagergyaca
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ccggggagct gaggggcarg gccgtagact cacggctgca cctgcaggga gcagcacgcc
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aaccccagca gtcctgggcc ccctgggaga gtgctcaacc tacagtggag ggagactgac
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cccgtttgag ctcggtatcc tagtgcacac gccttgcaag cgacggcgcc atg agt
                                                                      116
ctg act tcc agt tcc agc gta cga gtt gaa tgg atc gca gca gtt acc
Leu Thr Ser Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala Val Thr
            -20
                                -15
att gct gct ggg aca gct gca att ggt tat cta gct tac aaa aga ttt
                                                                      212
Ile Ala Ala Gly Thr Ala Ala Ile Gly Tyr Leu Ala Tyr Lys Arg Phe
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tat gtt aaa gat cat cga aat aaa gct atg ata aac ctt cac atc cag
                                                                     260
Tyr Val Lys Asp His Arg Asn Lys Ala Met Ile Asn Leu His Ile Gln
10
                    15
                                        20
aaa gac aac ccc aag ata gta cat gct ttt gac atg gag gat ttg gga
                                                                     308
Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp Leu Gly
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                                   35
gat aaa gct gtg tac tgc cgt tgt tgg agg tcc aaa aag ttc cca ttc
                                                                     356
Asp Lys Ala Val Tyr Cys Arg Cys Trp Arg Ser Lys Lys Phe Pro Phe
                                50
tgt gat ggg gct cac aca aaa cat aac gaa gag act gga gac aat gtg
                                                                     404
Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp Asn Val
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ggc cct ctg atc atc aag aaa aaa gaa act taaatggaca cttttgatgc
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Gly Pro Leu Ile Ile Lys Lys Lys Glu Thr
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                        80
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                                                                     514
ctgattcacc ttcgctggat tctaaatgtg gtatattgcm aactgcagct ttcacattta
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gtt	atg	gat	gtc	aca	<b>ggg</b>	gat	gaa	gag	Glu	Glu	TIE	LVS	Gln	Glu	Ile		
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			-55				~~+	-50		aat	att	act		tac	tat		156
aac	atg Met	ttg -	aag	aaa	tat	tct	Ude	Tic	720	Agn	Tle	Ala	Thr	Tvr	Tvr		
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MBII	T 111	шу 5	10	11011			-1-	15		-			20				
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Val	Lys	Leu	Val	Asp	Phe	Gly	Xaa	Xaa	Ala	Gln	Leu	Asp	Arg	Thr	Val		
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gtt	att	gcc	tgt	gat	gaa	aac	cca	sat	gcc	aca	tat -	gat	DEC	aar	Vaa		340
Va l	Ile	Ala	Cys	Asp	Glu	Asn	Pro	Xaa	Ala	Thr	Tyr	Asp	100	. Буз	Add		
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gac	ttg:	tgg	tct	ttg	ggt	ato	acc	gcc	att	gaa	Mot	yca 715	gaa Glu	999 61v	Ten		
Asp	Leu			Leu	. Gly	lle			. тте	: GIU	Met	115	. 61.4	. 017	Leu		
		105					110				a++ c			יכככם	gaatc		642
ccc	ctc	tct	gtg	aca	. tgc	acc	. cca	tga	gage	CCL	CLLC			.cccg	gaatc		
Pro	Leu		Val	Thr	Cys			)									
	120					125		+		+ +		atca	ttt	atto	agaget	;	702
cag	gegee	tcg	gctg	aagt	.ct a	agaa	grag	je da	aaaa	122C2	att	gate	raad	cato	agagct cattta	ı	762
gat	tggt	aaa	aaat	caca	ige c	ageg	acca acata	.g .ca	atte	aace	. cas	aaaa	cat	atto	cattta gatagaa	ı	822
tac	gaga	cca	acct	aatg	ag c	gace	iggic	,c gc		Juact	. cuc	ישכני					849
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r 10	
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Arg Asn Trp Leu Pro Thr Pro Pro Ala Thr Gly Pro Leu Pro Ser Ser	
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Ile Leu Phe Cys Asn Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg	
3.0 3.5 A.O	
25 30 35	

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Xaa Xaa Leu Gly Arg Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu 45 50 55	289
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tgcgcgaag atg cga aag gtg gtt ttr att acc ggg gct agc agt ggc att Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile	60 111
Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile -55 -50 -45	111
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Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile  -55  -50  -45  ggc ctg gcc ctc tgc aag cgg ctg ctg gcg gaa gat gat gag ctt cat Gly Leu Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His  -40  -35  ctg tgt ttg gcg tgc agg aat atg agc aag gca gaa gct gtc tgt gct Leu Cys Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala  -25  -20  -15  -10	111
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Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile  -55  -50  -45  ggc ctg gcc ctc tgc aag cgg ctg ctg gcg gaa gat gat gag ctt cat Gly Leu Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His  -40  -35  ctg tgt ttg gcg tgc agg aat atg agc aag gca gaa gct gtc tgt gct Leu Cys Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala  -25  -20  -15  -10  gct ctg ctg gcc tct cac ccc act gct gag gtc acc att gtc cag gtg Ala Leu Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val  -5  gat gtc agc aac ctg cag tca ttc ttc cgg gcc tcc aag gaa ctt aag Asp Val Ser Asn Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys  10  15  caa agg ttt cag aga tta gac tgt ata tat cta aat gct ggg atc atg Gln Arg Phe Gln Arg Leu Asp Cys Ile Tyr Leu Asn Ala Gly Ile Met  25  30  35  cct aat cca caa cta daat atc aaa gca ctt ttc ttc ggc ctc ttt tca	111 159 207 255 303
Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile  -55  -50  -45  ggc ctg gcc ctc tgc aag cgg ctg ctg gcg gaa gat gat gag ctt cat Gly Leu Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His  -40  -35  ctg tgt ttg gcg tgc agg aat atg agc aag gca gaa gct gtc tgt gct Leu Cys Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala  -25  -20  -15  -10  gct ctg ctg gcc tct cac ccc act gct gag gtc acc att gtc cag gtg Ala Leu Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val  -5  gat gtc agc aac ctg cag tca ttc tcc cgg gcc tcc aag gaa ctt aag Asp Val Ser Asn Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys  10  15  caa agg ttt cag aga tta gac tgt ata tat cta aat gct ggg atc atg Gln Arg Phe Gln Arg Leu Asp Cys Ile Tyr Leu Asn Ala Gly Ile Met  25  30  35  cct aat cca caa cta aat atc aaa gca ctt ttc ttc ggc ctc ttt tca Pro Asn Pro Gln Leu Asn Ile Lys Ala Leu Phe Phe Gly Leu Phe Ser	111 159 207 255 303
Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile  -55 -50 -45  ggc ctg gcc ctc tgc aag cgg ctg ctg gcg gaa gat gat gag ctt cat Gly Leu Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His  -40 -35 -30  ctg tgt ttg gcg tgc agg aat atg agc aag gca gaa gct gtc tgt gct Leu Cys Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala  -25 -20 -15 -10  gct ctg gcc tct cac ccc act gct gag gtc acc att gtc cag gtg Ala Leu Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val  -5 -5 -5 -5 -5 -5 -5 -5 -5 -5 -5 -5 -5	111 159 207 255 303 351
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		250					255				202		2 2 t	cad	acc	1071
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Leu		Lys	His	He	Arg		Thr	тте	GIII	ьуѕ	275	АБР	VPII	OIN	7114	
	265					270			200	~ a++		20 C	ccaa	aaca	a	1122
			ggc						age	actt	-999	ag g	ccaa	9900	<b>-</b>	
_		ser	Gly	ser		ьeu										
280					285	~++ <i>~</i>	2202	c ca	acct	gaga	aac	ataq	tga	accc	ttgtct	1182
aag	gatc	act	Lgag	acca	99 a	9110 2+24	aaya ctaa	a ta	faat	aaca	tac	gcat	ata	atca	cagcta	1242
cta	caaa	aag	aaat	aaaa ~=	a	aray	+~++	g rg	acta Tygu	aasa	aca	asaa	tta	caqt	gagetg	1302
CTC	agaa	gga	tgag	9599	ga 9	garc	aaa+	9 29	acca	agag	cct	atct	caa	aata	tgtata	1362
aga	itgt	gcc	actg	CACE	oo a	goot	999°	9 60	atra	cact	cta	aaac	att	gcat	accttc	1422
tat	ttaa	tat	atat	ataa	aa C	-aya	ataa	t an	atta	cate	ata	taca	ttt	gtaa	taaact	1482
							ctac	c ya	guug	yata	uca			J =		1504
atg	aact	alg	aaaa	aaad	aa d	ų.										

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<210> 372
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<sup>&</sup>lt;211> 765

<sup>&</sup>lt;212> DNA

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

<sup>&</sup>lt;221> CDS

<sup>&</sup>lt;222> 274..597

<sup>&</sup>lt;221> sig\_peptide

<sup>&</sup>lt;222> 274..399

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<210> 373

<211> 1041

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> 230..469

<221> sig\_peptide

<222> 230..307

<223> Von Heijne matrix score 4.90000009536743 seq VLCTNQVLITARA/VP

<221> polyA signal

<222> 1004..1009

<221> polyA\_site

<222> 1027..1040

WO 99/31236

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tcactccaga tacatggaaa gatggtgcta ggaataccac	agaaagtggt ggaagaaagc 180										
tgaatgaaaa taaagctttg acttcaaaaa aagccagaat	tgatccata atg gaa gaa 238										
	Met Glu Glu -25										
A seek took and the see and the see and set	<del></del>										
ata agt tot coa ott gta gaa ttt gta aaa gtt Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val	ccg cgc acc aar -ag										
-20 -15	-10										
gtt ctc att act gcc agg gct gtg cct aca aaa	aag gca tct gtg cga 334										
Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys	Lys Ala Ser Val Arg										
-5 1	5										
tgt gtg gaa aaa agg ttt tgg ata cca aaa act	aca agc aaa cat ctg 382										
Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr	Thr Ser Lys His Leu										
10 15 20	25 aar gat tit act tic 430										
tot aga tgt att gat gga att tot ggo ttt ota	aas gas see all										
Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu 30 35	40										
tgc ctt gaa ttt tca agg cat aga tgt caa ctt	<del>-</del> -										
Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu	Thr Glu										
45 50											
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cattattcat ataattctcc ccccaccact ttatttat	atactgcaaa aktgaraagg 719										
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tatataaatg tttcaagcca ttattgctga atggttcttt	agecaccado songario										
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tttaqaaaaa caaaaaaaaa ar	1041										
CCCayaaaaa Caaaaaaaaa xi											

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-25
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Ala Gly Ile Leu Phe Phe Thr Gly Trp Trp Ile Met Ile Asp Ala Ala
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Val Val Tyr Pro Lys Pro Glu Gln Leu Asn His Ala Phe His Thr Cys
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ggt gta ttt tcc aca ttg gct ttc ttc atg ata aat gct gta tcc aat
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Gly Val Phe Ser Thr Leu Ala Phe Phe Met Ile Asn Ala Val Ser Asn
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get cag gtg aga ggt gat age tat gaa age gge tgt tta gga aga aca
                                                                      350
Ala Gln Val Arg Gly Asp Ser Tyr Glu Ser Gly Cys Leu Gly Arg Thr
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ggt gct cga gtt tgg ctt ttc att ggt ttc atg ttg atg ttt ggg tca
                                                                      398
Gly Ala Arg Val Trp Leu Phe Ile Gly Phe Met Leu Met Phe Gly Ser
                                         60
ctt att gct tcc atg tgg att ctt ttt ggt gca tat gtt acc caa aat
                                                                      446
Leu Ile Ala Ser Met Trp Ile Leu Phe Gly Ala Tyr Val Thr Gln Asn
                                     75
act gat gtt tat ccg gga cta gct gtg ttt ttt caa aat gca ctt ata
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Thr Asp Val Tyr Pro Gly Leu Ala Val Phe Phe Gln Asn Ala Leu Ile
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                                                    95
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                                                                      542
Phe Phe Ser Thr Leu Ile Tyr Lys Phe Gly Arg Thr Glu Glu Leu Trp
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                                                110
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                                                                      955
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<210> 375
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<sup>&</sup>lt;211> 1250

<sup>&</sup>lt;212> DNA

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;220>

<sup>&</sup>lt;221> CDS

<sup>&</sup>lt;222> 36..425

<sup>&</sup>lt;221> sig\_peptide

<sup>&</sup>lt;222> 36..119

<sup>&</sup>lt;223> Von Heijne matrix score 11.6000003814697 seq LLLLVQLLRFLRA/DG

<sup>&</sup>lt;221> polyA signal

<sup>&</sup>lt;222> 1215..1220

<sup>&</sup>lt;221> polyA site

<sup>&</sup>lt;222> 1240..1250

<sup>&</sup>lt;400> 375

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ctg tgg ctg ctg gtg ctg tgc gcg ctg ctc ctg ctc ttg gtg cag ctg Leu Trp Leu Leu Val Leu Cys Ala Leu Leu Leu Leu Leu Val Gln Leu -20 -15 -10	101
ctg cgc ttc ctg agg gct gac ggc gac ctg acg cta cta tgg gcc gag Leu Arg Phe Leu Arg Ala Asp Gly Asp Leu Thr Leu Leu Trp Ala Glu -5 1 5 10	149
tgg cag gga cga cgc cca gaa tgg gag ctg act gat atg gtg gtg tgg Trp Gln Gly Arg Arg Pro Glu Trp Glu Leu Thr Asp Met Val Val Trp  15 20 25	197
gtg act gga gcc tcg agt gga att ggt gag gag ctg gct tac cag ttg Val Thr Gly Ala Ser Ser Gly Ile Gly Glu Glu Leu Ala Tyr Gln Leu 30 35	245
tot aaa ota gga gtt tot ott gtg otg toa goo aga aga gtg oat gag Ser Lys Leu Gly Val Ser Leu Val Leu Ser Ala Arg Arg Val His Glu 45 50 55	293
ctg gaa agg gtg aaa aga aga tgc cta gag aat ggc aat tta aaa gaa Leu Glu Arg Val Lys Arg Arg Cys Leu Glu Asn Gly Asn Leu Lys Glu 60 65 70	341
aaa gat ata ctt gtt ttg ccc ctt gac ctg acc gac act ggt tcc cat Lys Asp Ile Leu Val Leu Pro Leu Asp Leu Thr Asp Thr Gly Ser His 75 80 85 90	389
gaa agc ggc tac caa agc tgt tct cca gga att tgg tagaatcgac Glu Ser Gly Tyr Gln Ser Cys Ser Pro Gly Ile Trp	435
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gtctacagaa agctaatgag agcttaacta cttagggacg gtgtccttga caaaatgtgk	555
ketgeeteac atgategaga ngaarcaagg aaagattgtt actgtgaata geateetggg	615
tatcatatct gtacctcttt ccattggata ctgtgctagc aagcatgctc tccggggktk	675
ktttaatggc cttcraacag aacttgccac atacccargt ataatagttt ctaacatttg	735
cccaggacct gtgcaatcaa atattgtgga aaattcccta gctggagaag tcacaaagac	795
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<211> 947

<212> DNA

<213> Homo sapiens

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<222> 155..751

<221> sig\_peptide

<222> 155..340

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<221> polyA\_signal

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<211> 621

<212> DNA

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<220>

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<222> 46..585

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ctg tcg cgg gcg aac tca ctg ttc gcc ttc tcg ctg agc gtg atg gcs
                                                                     105
Leu Ser Arg Ala Asn Ser Leu Phe Ala Phe Ser Leu Ser Val Met Ala
                       -15
                                           -10
gcg ctc acc ttc ggc tgc ttc atc ayy acc gcc ttc aaa gac agg agc
                                                                     153
Ala Leu Thr Phe Gly Cys Phe Ile Xaa Thr Ala Phe Lys Asp Arg Ser
                         5
                    1
- 5
gtc ccg gtg cgg ctg cac gtc tcg cga atc atg cta aaa aat gta gaa
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Val Pro Val Arg Leu His Val Ser Arg Ile Met Leu Lys Asn Val Glu
                               2.0
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gat ttc act gga cct aga gaa aga agt gat ctg gga ttt atc aca ttt
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Asp Phe Thr Gly Pro Arg Glu Arg Ser Asp Leu Gly Phe Ile Thr Phe
        30
                            35
                                                                     297
gat ata act gct gat cta gag aat ata tit gat tgg aat gtt aag cag
Asp Ile Thr Ala Asp Leu Glu Asn Ile Phe Asp Trp Asn Val Lys Gln
                       50
ttg ttt ctt tat tta tca gca gaa tat tca aca aaa aat aat gct ctg
                                                                     345
Leu Phe Leu Tyr Leu Ser Ala Glu Tyr Ser Thr Lys Asn Asn Ala Leu
60
                   65
                                                                     393
aac caa ktt gtc cta tgg gac aag att gtt ttg aga ggt gat aat ccg
Asn Gln Xaa Val Leu Trp Asp Lys Ile Val Leu Arg Gly Asp Asn Pro
                                    85
                8.0
aag ctg ctg ctg aaa gat atg aaa aca aaa tat ttt ttc ttt gac gat
                                                                     441
Lys Leu Leu Lys Asp Met Lys Thr Lys Tyr Phe Phe Asp Asp
                               100
            95
                                                                     489
gga aat ggt ctc wag gga aac agg aat gtc act ttg acc ctg tct tgg
Gly Asn Gly Leu Xaa Gly Asn Arg Asn Val Thr Leu Thr Leu Ser Trp
                           115
aac gtc gta cca aat gct gga att cta cct ctt gtg aca gga tca gga
                                                                     537
Asn Val Val Pro Asn Ala Gly Ile Leu Pro Leu Val Thr Gly Ser Gly
                       130
                                                                     585
cac gta tct gtc cca ttt cca gat aca tat gaa ata acg aag agt tat
His Val Ser Val Pro Phe Pro Asp Thr Tyr Glu Ile Thr Lys Ser Tyr
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                                      150
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taaattatto tgaatttgaa acaaaaaaa aaaahm
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<210> 378
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<sup>&</sup>lt;211> 52

<sup>&</sup>lt;212> PRT

<sup>&</sup>lt;213> Homo sapiens

<sup>&</sup>lt;2205

<sup>&</sup>lt;221> SIGNAL

<sup>&</sup>lt;222> -20..-1

<sup>&</sup>lt;400> 378

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Phe Leu Ser Arg Gly Phe Trp Leu Cys Ala Ala His His Phe Ile His
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Pro Cys Leu Asp
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                      1
Glu Arg Arg Asp Thr Ala Pro Ser Gly Val Ser Arg Phe Cys Pro Pro
                                 20
Arg Lys Ser Cys His Asp Trp Ile Gly Pro Pro Asp Lys Tyr Ser Asn
      30
                             35
Leu Arg Pro Val His Phe Tyr Ile Pro Glu Asn Glu Ser Pro Leu Glu
   45
                          50
Gln Lys Leu Arg Lys Leu Arg Gln Glu Thr Gln Glu Trp Asn Gln Gln
                      65
Phe Trp Ala Asn Gln Asn Leu Thr Phe Ser Lys Glu Lys Glu Glu Phe
 75 80
                                    85
Ile His Ser Arg Leu Lys Thr Lys Gly Leu Gly Leu Arg Thr Glu Ser
90 95
                                100
Gly Gln Lys Ala Thr Leu Asn Ala Glu Glu Met Ala Asp Phe Tyr Lys
      110
                             115 120
Glu Phe Leu Ser Lys Asn Phe Gln Lys His Met Tyr Tyr Asn Arg Asp
 125
                         130
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Trp Tyr Lys Arg Asn Phe Ala Ile Thr Phe Phe Met Gly Lys Val Ala
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Asn
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<222> -14..-1

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Lys Ser Xaa Xaa Met Xaa Leu Ile Arg Ser Val Arg Thr Val Met Arg
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Glu Glu Leu Thr Leu Leu Phe His Gly Thr Leu Gln Leu Gly Gln Ala
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Leu Asn Gly Val Tyr Arg Thr Thr Glu Gly Arg Leu Thr Lys Ala Arg
                          35
Asn Ser Leu Gly Leu Tyr Gly Arg Thr Ile Glu Leu Leu Gly Gln Glu
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Val Ser Arg Gly Arg Asp Ala Ala Gln Glu Leu Arg Ala Ser Leu Leu
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                  65
Glu Thr Gln Met Glu Glu Asp Ile Leu Xaa Leu Gln Ala Xaa Ala Thr
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              80
Ala Glu Val Leu Gly Glu Val Ala Gln Ala Gln Lys Val Leu Arg Asp
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                             100
           95
Ser Val Gln Arg Leu Xaa Xaa Gln Leu Xaa Xaa Ala Trp Leu Gly Pro
                         115
                                           120
Ala Tyr Arg Lys Phe Glu Val Leu Lys Ala Pro Pro Xaa Lys Gln Asn
                      130
His Ile Leu Trp Ala Leu Thr Gly His Val Xaa Arg Gln Xaa Arg Glu
                 145
                                    150
Met Val Ala Gln Gln Xaa Xaa Leu Xaa Gln Ile Gln Glu Lys Leu His
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              160
Thr Ala Ala Leu Pro Ala
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 <211> 160
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<222> -55..-1

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<400> 383

<210> 384 <211> 64 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -22..-1 <400> 384 Met Ile Ser Arg Gln Le

Met Ile Ser Arg Gln Leu Arg Ser Leu Ser Cys Leu Cys Pro Ala Leu -20 -15 -10

Phe Pro Gly Thr Ser Ser Phe Ile Val Ala Leu Ser Ser Pro Ala Asp

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```
Leu Tyr Ile Pro Xaa Arg Xaa Arg Ser Asp Glu Leu Val Phe Glu Ser
        15 20 25
Gln Lys Gly Ser Ala Met Glu Leu Ala Val Ile Thr Val Xaa Gly Val
       30 35
<210> 385
<211> 27
<212> PRT
<213> Homo sapiens
<221> SIGNAL
<222> -15..-1
<400> 385
Met Gly Phe Leu Xaa Leu Met Thr Leu Thr Thr His Val His Ser Ser
Ala Lys Pro Asn Glu Gln Pro Trp Leu Leu Asn
   5
                       10
<210> 386
<211> 186
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 386
Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile
 -20 -15 -10
Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser
-5 1 5
Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp
 15 20 25
Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro
 30 35 40
Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly
 45 50 55
Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Xaa Ser Xaa Lys
60 65 70 75
Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser
      80 85 90
Pro Ser Thr Xaa Val His Xaa Arg Pro Xaa Xaa Pro Ser Xaa His Leu
   95 100 105
Val Phe Met Arg Met Thr Pro Ser Ser Met Met Asn Thr Pro Ser Gly
                   115 120
Asn Xaa Gly Cys Trp Ser Gln Leu Cys Cys Ser Ser Gln Ala Ser Ser
               130 135
Ser Ser Pro Val Ala Ser Ala Gly Ser Cys Pro Gly Tyr Ala Gly Ile
            145 150
 Ile Ala Gly Glu Ser Ile Arg Asn Arg Ser
```

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<210> 387
<211> 179
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 387
Met Glu Thr Gly Ala Leu Arg Arg Pro Gln Leu Leu Pro Leu Leu Leu
                   -20
Leu Leu Cys Gly Pro Ser Gln Asp Gln Cys Arg Pro Val Leu Gln Asn
Leu Leu Gln Ser Pro Gly Leu Thr Trp Ser Leu Glu Val Pro Thr Gly
                               15
Arg Glu Gly Lys Glu Gly Gly Asp Arg Gly Pro Gly Leu Xaa Gly Ala
                           30
Thr Pro Ala Arg Ser Pro Gln Gly Lys Glu Met Gly Arg Gln Arg Thr
Arg Lys Val Lys Gly Pro Ala Trp Xaa His Thr Ala Asn Gln Glu Leu
                   60
                                       65
Asn Arg Met Arg Ser Leu Ser Ser Gly Ser Val Pro Val Gly His Leu
                                   80
Glu Gly Gly Thr Val Lys Leu Gln Lys Asp Thr Gly Leu His Ser Cys
                              95
Xaa Asp Gly Met Ala Ser Leu Glu Gly Thr Pro Ala Ser Val Leu Ala
                          110
Asp Ala Cys Pro Gly Phe His Asp Val Xaa Val Gln Xaa Ala Leu Phe
                    125
                                          130
Gly Leu Ser Gly Xaa Xaa Leu Trp Leu Lys Thr His Phe Cys Leu Ser
135 140
                               145
Ile Xaa Leu
<210> 388
<211> 150
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 388
Met Ala Thr Thr Val Pro Asp Gly Cys Arg Asn Gly Leu Lys Ser Lys
                   -50
                                       -45
Tyr Tyr Arg Leu Cys Asp Lys Ala Glu Ala Trp Gly Ile Val Leu Glu
               - 35
                                   -30
Thr Val Ala Thr Ala Gly Val Val Thr Ser Val Ala Phe Met Leu Thr
                               ~15
Leu Pro Ile Leu Val Cys Lys Val Gln Asp Ser Asn Arg Arg Lys Met
Leu Pro Thr Gln Phe Leu Phe Leu Leu Gly Val Leu Gly Ile Phe Gly
                   15
Leu Thr Phe Ala Phe Ile Ile Gly Leu Asp Gly Ser Thr Gly Pro Thr
              30
                                  3.5
Arg Phe Phe Leu Phe Gly Ile Leu Phe Ser Ile Cys Phe Ser Cys Leu
                              50
Leu Ala Hiş Ala Val Ser Leu Thr Lys Leu Val Arg Gly Arg Lys Ala
                    . 65
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Pro Phe Pro Val Gly Asp Ser Gly Ser Gly Arg Gly Leu Gln Pro Ser 75 80 Pro Gly Cys Tyr Arg Tyr <210> 389 <211> 236 <212> PRT <213 > Homo sapiens <220> <221> SIGNAL <222> -31..-1 <400> 389 Met Leu Ser Lys Gly Leu Lys Arg Lys Arg Glu Glu Glu Glu Lys -25 -20 Glu Pro Leu Ala Val Asp Ser Trp Trp Leu Asp Pro Gly His Ala Ala -10 -5 Val Ala Gln Ala Pro Pro Ala Val Ala Ser Ser Leu Phe Asp Leu 5 10 15 Ser Val Leu Lys Leu His His Ser Leu Gln Xaa Ser Xaa Pro Asp Leu 25 30 Arg His Leu Val Leu Val Xaa Asn Thr Leu Arg Arg Ile Gln Ala Ser 35 40 45 Met Ala Pro Ala Ala Ala Leu Pro Pro Val Pro Thr Pro Pro Ala Ala 50 55 60 65 Pro Xaa Val Ala Asp Asn Leu Leu Ala Ser Ser Asp Ala Ala Leu Ser 75 80 7.0 Ala Ser Met Ala Xaa Leu Leu Glu Asp Leu Ser His Ile Glu Gly Leu 90 95 85 Ser Gln Ala Pro Gln Pro Leu Ala Asp Glu Gly Pro Pro Gly Arg Ser 100 105 110 Ile Gly Gly Xaa Pro Pro Xaa Leu Gly Ala Leu Asp Leu Leu Gly Pro 120 125 115 Ala Thr Gly Cys Leu Leu Asp Asn Gly Leu Glu Gly Leu Phe Glu Asp 130 135 140 Ile Asp Thr Ser Met Tyr Asp Asn Glu Leu Trp Ala Pro Ala Ser Glu 150 155 160 Gly Leu Lys Pro Gly Pro Glu Asp Gly Pro Gly Lys Glu Glu Ala Pro 165 170 175 Glu Leu Asp Glu Ala Glu Leu Asp Tyr Leu Met Asp Val Leu Val Gly 180 185 190 Thr Gln Ala Leu Glu Arg Pro Pro Gly Pro Gly Arg 200 <210> 390 <211> 149 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -100..-1 <400> 390 Met Glu Thr Leu Tyr Arg Val Pro Phe Leu Val Leu Glu Cys Pro Asn

- 95

-90

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```
Leu Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr
     -80 -75 -70
Val Tyr Ala Leu Val Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Ile
        -65 -60
Ile Tyr Asp Val Ile Val Glu Pro Pro Ser Val Gly Ser Met Thr Asp
Glu His Gly His Gln Arg Pro Val Ala Phe Leu Ala Tyr Arg Val Asn
 -35 -30 -25
Gly Gln Tyr Ile Met Glu Gly Leu Ala Ser Ser Phe Leu Phe Thr Met
-20 -15 -10 -5
Gly Gly Leu Gly Phe Ile Ile Leu Asp Gly Ser Asn Ala Pro Asn Ile
                             10
Pro Lys Leu Asn Arg Phe Leu Leu Leu Phe Ile Gly Phe Val Cys Val
         20 25
Leu Xaa Ser Phe Xaa Xaa Ala Arg Val Phe Met Arg Met Lys Leu Pro
30 35
Gly Tyr Leu Met Gly
<210> 391
<211> 69
<212> PRT
<213 > Homo sapiens
<220>
<221> SIGNAL
<222> -49..-1
<400> 391
Met Pro Phe His Phe Pro Phe Leu Gly Phe Val Cys Leu His Leu His
      -45 -40
Leu Thr Pro Cys Leu Thr Val Pro Arg Arg Pro Leu Phe Leu Leu
 -30 -25 -20
His Leu Cys Pro His Leu Pro Phe Leu Leu Leu Ser Cys Val Gly
-15 -10 -5
Xaa Xaa Pro Ser Cys Leu Pro Ser Ser Ser Thr Cys Val Ser Leu His
1 5
                     10
Phe Phe Ile Pro Asp
         20
<210> 392
<211> 241
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 392
Met Gly Thr Ala Ser Arg Ser Asn Ile Ala Arg His Leu Gln Thr Asn
    -25 -20 -15
Leu Ile Leu Phe Cys Val Gly Ala Val Gly Ala Cys Thr Leu Ser Val
                     -5
         -10
Thr Gln Pro Trp Tyr Leu Glu Val Asp Tyr Thr His Glu Ala Val Thr
```

5 10

15

Ile Lys Cys Thr Phe Ser Ala Thr Gly Cys Pro Ser Glu Gln Pro Thr

Cys Leu Trp Phe Arg Tyr Gly Ala His Gln Pro Glu Asn Leu Cys Leu 40 Asp Gly Cys Lys Ser Glu Ala Xaa Lys Phe Thr Val Arg Glu Ala Leu 55 60 Lys Glu Asn Gln Val Ser Leu Thr Val Asn Arg Val Thr Ser Asn Asp 75 70 Ser Ala Ile Tyr Ile Cys Gly Ile Ala Phe Pro Ser Val Pro Glu Ala 90 Arg Ala Lys Gln Thr Gly Gly Gly Thr Thr Leu Val Val Arg Glu Ile 110 105 Lys Leu Leu Ser Lys Glu Leu Arg Ser Phe Leu Thr Ala Leu Val Ser 125 120 Leu Leu Ser Val Tyr Val Thr Gly Val Cys Val Ala Phe Ile Leu Leu 140 135 Ser Lys Ser Lys Ser Asn Pro Leu Arg Asn Lys Glu Ile Lys Glu Asp 150 155 Ser Gln Lys Lys Lys Ser Ala Arg Arg Ile Phe Gln Glu Ile Ala Gln **165 17**0 175 Glu Leu Tyr His Lys Arg His Val Glu Thr Asn Gln Gln Ser Glu Lys 185 190 Asp Asn Asn Thr Tyr Glu Asn Arg Arg Val Leu Ser Asn Tyr Glu Arg 205 200

<210> 393 <211> 47 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -30..-1

Met Asn Cys Asn Val Val Ser Glu Arg Gly Lys Trp Leu Glu Val Glu
-30 -25 -25 -20 -15

Cys Ser Leu Met Thr Cys Thr Thr Leu Ile Asn Ala Ser Ala Ile Ser
-10 -5 -5 1

Thr Asn Thr Leu Thr Asp Met Gly Ser Phe Asp Arg Glu Ser
5 10 -15

<210> 394 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1

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30

35

Ser

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<210> 395
<211> 73
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
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<400> 395

<210> 396 <211> 60 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1 <400> 396 Met Pro Cys Pro Thr Trp Thr Cys Leu Lys Ser Phe Pro Ser Pro Thr -10 - 5 Ser Ser His Ala Ser Ser Leu His Leu Pro Pro Ser Cys Thr Arg Leu 10 Thr Leu Thr Gln Thr Leu Arg Thr Gly Met His Leu Ser Arg Ala Leu 20 25 Gln Gly Thr Leu Thr Arg Leu Gln Ser Thr Pro Ala

-70 -75 Asp Ser Cys Phe Gln Asp Leu Lys Glu Ser Arg Leu Val Glu Asp Thr -50 -60 -55 Phe Thr Ile Asp Glu Val Ser Glu Val Leu Asn Gly Leu Gln Ala Val -35 -40 Val His Ser Glu Val Glu Ser Glu Leu Ile Asn Thr Ala Tyr Thr Asn -20 -25 Val Leu Leu Leu Arg Gln Leu Phe Ala Gln Ala Glu Lys Trp Tyr Leu -10 -5 Lys Leu Gln Thr Asp Ile Ser Glu Leu Glu Asn Arg Glu Leu Leu Glu 10 15 Gln Xaa Ala Glu Phe Glu Lys Ala Xaa Ile Thr Ser Ser Asn Lys Lys 30 25 Pro Ile Leu Xaa Val Thr Xaa Pro Lys Leu Ala Pro Leu Asn Glu Gly 40 45 Gly Thr Ala Lys Leu Leu Asn Lys Val Ile Cys Ile Ile Leu Arg Asn 60 √5.5 Gly Lys Ser Leu Ile Leu Ser Cys His Cys Leu Gly Trp Arg Asn Lys Ser Gly Arg Phe Val Ser Gly Pro Leu Arg Ile Ile Ser Pro Leu Gln 90

<210> 398 <211> 149 <212> PRT <213> Homo sapiens <220>

<221> SIGNAL <222> -72..-1

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<400> 398 Met Asn Leu Phe Ile Met Tyr Met Ala Gly Asn Thr Ile Ser Ile Phe -65 Pro Thr Met Met Val Cys Met Met Ala Trp Arg Pro 11e Gln Ala Leu -45 -50 Met Ala Ile Ser Ala Thr Phe Lys Met Leu Glu Ser Ser Ser Gln Lys -30 -35 Phe Leu Gln Gly Leu Val Tyr Leu Ile Gly Asn Leu Met Gly Leu Ala -15 -10 Leu Ala Val Tyr Lys Cys Gln Ser Met Gly Leu Leu Pro Thr His Ala 1 Ser Asp Trp Leu Ala Phe Ile Glu Pro Pro Glu Arg Met Glu Ser Val 20 15 Val Glu Asp Cys Phe Cys Glu His Glu Lys Ala Ala Pro Gly Pro Tyr 3.5 30 Val Phe Gly Ser Tyr Leu His Pro Ser Leu Ser Pro Val Ala Pro Gln 50 45 His Thr Leu Lys Leu Ile Thr Tyr Val Lys Lys Asn Gln Lys Thr Leu 65 Phe Ser Met Val Gly

<210> 399 <211> 73 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -20..-1
<400> 399
Met Thr Pro Leu Leu Thr Leu Ile Leu Val Val Leu Met Gly Leu Pro
-20 -15 -10 -5
Leu Ala Gln Ala Leu Asp Cys His Val Cys Ala Tyr Asn Gly Asp Asn
          1 5
Cys Phe Asn Pro Met Arg Cys Pro Ala Met Val Ala Tyr Cys Met Thr
 15 20
Thr Arg Thr Tyr Tyr Thr Pro Thr Arg Met Lys Val Ser Lys Ser Cys
 30 35
Val Pro Arg Cys Phe Glu Xaa Cys Val
45 50
<210> 400
<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -20..-1
<400> 400
Met Asn Leu His Phe Pro Gln Trp Phe Val His Ser Ser Ala Leu Gly
-20 -15 -10 -5
Leu Val Leu Ala Pro Pro Phe Ser Ser Pro Gly Thr Asp Pro Thr Phe
          1 5
Pro Cys Ile Tyr Cys Arg Leu Leu Asn Met Ile Met Thr Arg Leu Ala
 15
            20
Phe Ser Phe Ile Thr Cys Leu Cys Pro Asn Leu Lys Glu Val Cys Leu
 30 35 40
Ile Leu Pro Glu Lys Asn Cys Asn Ser Arg His Ala Gly Phe Val Gly
45 50
                      55
Pro Xaa Lys Leu Arg Gln
           65
<210> 401
<211> 78
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 401
Met Cys Pro Val Phe Ser Lys Gln Leu Leu Ala Cys Gly Ser Leu Leu
  -20 -15 -10
Pro Gly Leu Trp Gln His Leu Thr Ala Asn His Trp Pro Pro Phe Ser
             1
                   5
Xaa Phe Leu Cys Thr Val Cys Ser Gly Ser Ser Glu Gln Ile Ser Glu
               20
       15
Tyr Thr Ala Ser Ala Thr Pro Pro Leu Cys Arg Ser Leu Asn Gln Glu
```

30 35

Pro Phe Val Ser Arg Ala Ile Arg Pro Lys Tyr Ser Ile Thr

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50

<210> 402 <211> 65 <212> PRT

<213> Homo sapiens

<220> <221> SIGNAL <222> -28..-1

45

<400> 402 Met Gly Lys Gly His Gln Arg Pro Trp Trp Lys Val Leu Pro Leu Ser -20 Cys Phe Leu Val Ala Leu Ile Ile Trp Cys Tyr Leu Arg Glu Glu Ser - 5 Glu Ala Asp Gln Trp Leu Arg Gln Val Trp Gly Glu Val Pro Glu Pro 15 1.0 Ser Asp Arg Ser Glu Glu Pro Glu Thr Pro Ala Ala Tyr Arg Ala Arg 30 25 Thr

<210> 403 <211> 211 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> -27..-1 Met Leu Leu Ser Ile Thr Thr Ala Tyr Thr Gly Leu Glu Leu Thr -20 -25 Phe Phe Ser Gly Val Tyr Gly Thr Cys Ile Gly Ala Thr Asn Lys Phe - 5 Gly Ala Glu Glu Xaa Ser Leu Ile Gly Leu Ser Gly Ile Phe Ile Gly 15 10 Ile Gly Glu Ile Leu Gly Gly Ser Leu Phe Gly Leu Leu Ser Lys Asn 30 Asn Arg Phe Gly Arg Asn Pro Val Val Leu Leu Gly Ile Leu Val His 45 Phe Ile Ala Phe Tyr Leu Ile Phe Leu Asn Met Pro Gly Asp Ala Pro 60 Ile Ala Pro Val Lys Gly Thr Asp Ser Ser Ala Tyr Ile Lys Ser Ser 80 75 Lys Xaa Phe Ala Ile Leu Cys Xaa Phe Leu Xaa Gly Leu Gly Asn Ser 95 90 Cys Phe Asn Thr Xaa Leu Leu Xaa Ile Xaa Gly Phe Leu Tyr Ser Glu 110 115 105 Xaa Ser Ala Pro Xaa Phe Ala Ile Phe Asn Phe Val Gln Ser Ile Cys 125 120 Ala Ala Val Ala Phe Phe Tyr Ser Asn Tyr Leu Leu Leu His Trp Gln 140 Leu Leu Val Met Val Ile Phe Gly Phe Xaa Gly Thr Ile Ser Phe Phe 160

Thr Val Glu Trp Glu Xaa Ala Ala Phe Val Xaa Arg Gly Ser Asp Tyr

175

155

Arg Ser Ile

<210> 405

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<210> 404
<211> 123
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -80..-1
<400> 404
Met Ser Thr Trp Tyr Leu Ala Leu Asn Lys Ser Tyr Lys Asn Lys Asp
-80 -75 -70 -65
Ser Val Arg Ile Tyr Leu Ser Leu Cys Thr Val Ser Ile Lys Phe Thr
         -60 -55 -50
Tyr Phe His Asp Ile Gln Thr Asn Cys Leu Thr Thr Trp Lys His Ser
      -45 -40 -35
Arg Cys Arg Phe Tyr Trp Ala Phe Gly Gly Ser Ile Leu Gln His Ser
   ~30 -25 -20
Val Asp Pro Leu Val Leu Phe Leu Ser Leu Ala Leu Leu Val Thr Pro
-15 -10 -5
Thr Ser Thr Pro Ser Ala Lys Ile Gln Ser Leu Gln Ile Asp Leu Pro
1 5 10 15
Gly Gly Trp Arg Leu Ala Thr Asp Arg Ile Phe Thr Leu Ser Pro Val
   20 25
Pro Met Asp Xaa Pro Leu Ile Leu His Gln Leu
    35
                   40
```

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<211> 86
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
Met Glu Lys Ser Trp Met Leu Trp Asn Phe Val Glu Arg Trp Leu Ile
-25 -20 -15
Ala Leu Ala Ser Trp Ser Trp Ala Leu Cys Arg Ile Ser Leu Leu Pro
             -5
                             1 5
Leu Ile Val Thr Phe His Leu Tyr Gly Gly Ile Ile Leu Leu Leu
                      15
Ile Phe Ile Ser Ile Xaa Gly Ile Leu Tyr Lys Phe Xaa Asp Val Leu
 25 30
                               35
Leu Tyr Phe Pro Xaa Gln Xaa Ser Ser Ser Arg Leu Tyr Asp Ser His
                          50 '
Ala His Trp Xaa Ser Xaa
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<210> 406 <211> 162 <212> PRT <213 > Homo sapiens

125

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<220>
<221> SIGNAL
<222> -31..-1
<400> 406
Met Ala Ala Arp Pro Ser Gly Pro Xaa Ala Pro Glu Ala Val Thr
                    -25 . -20
Ala Arg Leu Val Gly Val Leu Trp Phe Val Ser Val Thr Thr Gly Pro
       -10
                                  - 5
Trp Gly Ala Val Ala Thr Ser Ala Gly Gly Glu Glu Ser Leu Lys Cys
                           10
Glu Asp Leu Lys Val Gly Gln Tyr Ile Cys Lys Asp Pro Lys Ile Asn
                       25
Asp Ala Thr Gln Glu Pro Val Asn Cys Thr Asn Tyr Thr Ala His Val
 35 40
Ser Cys Phe Pro Ala Pro Asn Ile Thr Cys Lys Asp Ser Ser Gly Asn
50 55
Glu Thr His Phe Thr Gly Asn Glu Val Gly Phe Phe Lys Pro Ile Ser
            70
                               75
Cys Arg Asn Val Asn Gly Tyr Ser Tyr Asn Glu Gln Ser His Val Ser
                           90
         8.5
Phe Ser Trp Met Val Gly Ser Arg Ser Ile Leu Pro Trp Ile Pro Cys
                                110
 100 105
Phe Gly Phe Val Lys Xaa Xaa His Cys Arg Val Xaa Trp Asn Trp Glu
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<210> 407 <211> 98 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -37..-1

120

115

Pro Asn 130

<400> 407 Met Ala Ser Leu Leu Cys Cys Gly Pro Lys Leu Ala Ala Cys Gly Ile -30 Val Leu Ser Ala Trp Gly Val Ile Met Leu Ile Met Leu Gly Ile Phe -15 -10 Phe Asn Val His Ser Ala Val Leu Ile Glu Asp Val Pro Phe Thr Glu 1 Lys Asp Phe Glu Asn Gly Pro Gln Asn Ile Tyr Asn Leu Tyr Xaa Gln 20 15 Xaa Ser Tyr Asn Cys Phe Ile Ala Ala Gly Leu Tyr Leu Leu Leu Gly 35 Gly Phe Ser Phe Cys Gln Xaa Arg Leu Asn Lys Arg Lys Glu Tyr Met Val Arg 60

<210> 408 <211> 70 <212> PRT <213> Homo sapiens

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<220>
 <221> SIGNAL
 <222> -15..-1
<400> 408
Met Arg Phe Leu Pro Cys Cys Leu Leu Trp Ser Val Phe Asn Pro Glu
-15 -10 -5
Ser Leu Asn Cys His Tyr Phe Xaa Xaa Glu Xaa Cys Ile Phe Xaa Ser
      5
                   10
Leu Gln Tyr Tyr Glu Ile Ser Leu Gln Glu Lys Leu Leu Gly Phe Leu
                25
                            30
Trp Leu Cys Phe Leu Ser Tyr Phe Phe Arg Ala Val Tyr Phe Leu Ile
 35 40
Asp Phe Ser Ser Phe Thr
<210> 409
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -45..-1
<400> 409
Met His Ser Leu Phe Ile Ala Ser Leu Lys Val Leu Phe Tyr Tyr Ser
-45 -40
                   -35 -30
Phe Ser Phe Arg Phe Asn Trp Phe Asp Cys Leu Leu His Asn Leu Gly
      -25 -20 -15
Glu Asn Phe Leu Ser Leu Leu Ser Lys Ser Cys Ser Ala Asp Pro Ser
  -10 -5
Gly Ser Thr Phe Met Arg Asp Ile Glu Thr Asn Lys
 5 10
<210> 410
<211> 39
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -22..-1
<400> 410
Met Pro Glu Ala Val Glu Gln Ser Ala His Leu Phe Val Thr Trp Ser
 -20 -15 -10
Ser Gln Arg Ala Leu Ser His Pro Ala Pro Phe Leu Thr Xaa Xaa Lys
-5 1
                      5
Asn Pro Phe Leu Trp Lys Leu
<210> 411
<211> 51
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<212> PRT

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<213 > Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 411
Met Ala Phe Gln Ser Leu Leu Glu Met Lys Phe Phe Leu Cys Ala Ala
    -20 -15 -10
Phe Pro Leu Gly Ala Gly Val Lys Met Phe His Tyr Leu Gly Pro Gly
                    1
Lys Pro Leu Xaa Gln Ala Ser Pro Ser Pro His Pro His Arg Xaa Arg
10 15
                       20
Ile Trp Pro
<210> 412
<211> 95
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -48..-1
<400> 412
Met Ala Ser Ser His Trp Asn Glu Thr Thr Thr Ser Val Tyr Gln Tyr
    -45 -40 -35
Leu Gly Phe Gln Val Gln Lys Ile Tyr Pro Phe His Asp Asn Trp Asn
                     -25
 -30
Thr Ala Cys Phe Val Ile Leu Leu Leu Phe Ile Phe Thr Val Val Ser
                 -10
 -15
Leu Val Val Leu Ala Phe Leu Tyr Glu Val Leu Xaa Xaa Cys Cys Cys
                             10 15
Val Lys Asn Lys Thr Val Lys Asp Leu Lys Ser Glu Pro Asn Pro Leu
    20 25
Xaa Xaa Met Met Asp Asn Ile Arg Lys Arg Glu Thr Glu Val Val
    35
<210> 413
<211> 60
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1
Met Asp Glu Tyr Ser Trp Trp Cys His Val Leu Glu Val Val Lys Gly
                    -25
                              - 20
    -30
Gln Met Phe Thr Phe Ile Asn Ile Thr Leu Trp Leu Gly Ser Leu Cys
                              - 5
                    -10
Gln Arg Phe Phe Tyr Ala Ser Gly Thr Tyr Phe Leu Ile Tyr Ile Ser
```

1 5 10

20

Thr Val Thr Pro Ser Trp Arg Leu Cys Leu Val Ser

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<210> 414
<211> 170
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -79..-1
<400> 414
Met Glu Asp Pro Asn Pro Glu Glu Asn Met Lys Gln Gln Asp Ser Pro
       -75 -70 -65
Lys Glu Arg Ser Pro Gln Ser Pro Gly Gly Asn Ile Cys His Leu Gly
    -60 -55 -50
Ala Pro Lys Cys Thr Arg Cys Leu Ile Thr Phe Ala Asp Ser Lys Phe
 -45 - -40
                        -35
Gln Glu Arg His Met Lys Arg Glu His Pro Ala Asp Phe Val Ala Gln
 -30 -25 -20
Lys Leu Gln Gly Val Leu Phe Ile Cys Phe Thr Cys Ala Arg Ser Phe
-15 -10 -5 <sub>1</sub>
Pro Ser Ser Lys Ala Xaa Xaa Thr His Gln Arg Ser His Gly Pro Xaa
   5 10 15
Ala Lys Pro Thr Leu Pro Val Ala Thr Thr Thr Ala Gln Pro Thr Phe
20 25
                        30
Pro Cys Pro Asp Cys Gly Lys Thr Phe Gly Gln Ala Val Ser Leu Xaa
 35 40
                     45
Arg His Xaa Gln Xaa His Glu Val Arg Ala Pro Pro Gly Thr Phe Ala
50 55
                 60
Cys Thr Xaa Cys Gly Gln Asp Phe Ala Gln Glu Xaa Gly Leu His Gln
      70
                  75
His Tyr Ile Arg His Ala Arg Gly Gly Leu
      85
<210> 415
<211> 190
<212> PRT
<213 > Homo sapiens
<220>
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<221> SIGNAL <222> -82..-1 <400> 415 Met Tyr Val Trp Pro Cys Ala Val Val Leu Ala Gln Tyr Leu Trp Phe ~80 -75 -70 His Arg Arg Ser Leu Pro Gly Lys Ala Ile Leu Glu Ile Gly Ala Gly -60 -55 Val Ser Leu Pro Gly Ile Leu Ala Ala Lys Cys Gly Ala Glu Val Ile -50 -45 -40 Leu Ser Asp Ser Ser Glu Leu Pro His Cys Leu Glu Val Cys Arg Gln -30 -25 -20 Ser Cys Gln Met Asn Asn Leu Pro His Leu Gln Val Val Gly Leu Thr -15 -10 -5 Trp Gly His Ile Ser Trp Asp Leu Leu Ala Leu Pro Pro Gln Asp Ile 1 5 10 Ile Leu Ala Ser Asp Val Phe Phe Glu Pro Glu Xaa Phe Glu Asp Ile 15 20 25 30 Leu Ala Thr Ile Tyr Phe Leu Met His Lys Asn Pro Lys Val Gln Leu 35 40

<211> 114 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1 <400> 416 Met Met Ala Ala Val Pro Pro Gly Leu Glu Pro Trp Asn Arg Val Arg -60 -55 -50 -45 Ile Pro Lys Ala Gly Asn Arg Ser Ala Val Thr Val Gln Asn Pro Gly -35 -40 Ala Ala Leu Asp Leu Cys Ile Ala Ala Val Ile Lys Glu Cys His Leu -25 -20 -15 Val Ile Leu Ser Leu Lys Ser Gln Thr Leu Asp Ala Glu Thr Asp Val -10 -5 Leu Cys Ala Val Leu Tyr Ser Asn His Asn Arg Met Gly Arg His Lys 15 20 10 Pro His Leu Ala Leu Lys Gln Val Glu Gln Cys Leu Lys Arg Leu Lys 30 25 Asn Met Asn Leu Glu Gly Ser Ile Gln Asp Leu Phe Glu Leu Phe Ser

<210> 417 <211> 161 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> ~108..-1

Ser Lys

<210> 416

<400> 417 Met Thr Ser Gly Gln Ala Arg Ala Ser Xaa Gln Ser Pro Gln Ala Leu -105 -100 -95 Glu Asp Ser Gly Pro Val Asn Ile Ser Val Ser Ile Thr Leu Thr Leu -85 - 90 Asp Pro Leu Lys Pro Phe Gly Gly Tyr Ser Arg Asn Val Thr His Leu -75 -70 -65 Tyr Ser Thr Ile Leu Gly His Gln Ile Gly Leu Ser Gly Arg Glu Ala -50 -45 -55 His Glu Glu Ile Asn Ile Thr Phe Thr Leu Pro Thr Ala Trp Ser Ser -35 -30 -40 Asp Asp Cys Ala Leu His Gly His Cys Glu Gln Val Val Phe Thr Ala -20 Cys Met Thr Leu Thr Ala Ser Pro Gly Val Phe Pro Ser Leu Tyr Ser

```
-10
                           - 5
 His Arg Thr Val Phe Leu Thr Arg Thr Ala Thr Pro Arg Ser Gly Thr
                 10
                                   . 15
 Arg Ser Ser Gln Leu Pro Glu Met Pro Thr Gln Asn Thr Pro Lys Ile
                           30
 Thr Ile Leu Ser Gly Val Ile Arg Gly Pro Leu Glu Lys Ser Ile Met
                             4.5
 Leu
 <210> 418
 <211> 67
 <212> PRT
 <213> Homo sapiens
<220>
 <221> SIGNAL
<222> -21..-1
<400> 418
Met Leu Gly Gly Asp His Arg Ala Leu Leu Leu Lys Ile Trp Leu Leu
                      - 15
                                          -10
Gln Arg Pro Glu Ser Gln Glu Gly Leu Leu Pro Gly Arg Leu Val Val
Met Glu Arg Arg Val Lys Asn Asp Leu Met Ser Phe Leu Ser Thr Val
                       20
Leu Leu Ser Phe His Ser Ser Asn Ala Arg Val Ser His Cys Glu Pro
Leu Arg Met
  45
<210> 419
<211> 332
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -32..-1
<400> 419
Met Ile Xaa Leu Arg Asp Thr Ala Ala Ser Leu Arg Leu Glu Arg Asp
   -30 -25
                                             -20
Thr Arg Gln Leu Pro Leu Leu Thr Ser Ala Leu His Gly Leu Gln Gln
                   -10
                                         - 5
Gln His Pro Ala Phe Ser Gly Val Ala Arg Leu Ala Lys Arg Trp Val
                                  10
Arg Ala Gln Leu Leu Gly Glu Gly Phe Ala Asp Glu Ser Leu Asp Leu
                             25
Val Ala Ala Leu Phe Leu His Pro Glu Pro Phe Thr Pro Pro Ser
                          40
Ser Pro Gln Val Gly Phe Leu Arg Phe Leu Phe Leu Val Ser Thr Phe
                     55
Asp Trp Lys Asn Asn Pro Leu Phe Val Asn Leu Asn Asn Glu Leu Thr
                  70
                                     75
Val Glu Glu Gln Val Glu Ile Arg Ser Gly Phe Leu Ala Ala Arg Ala
                                 90
Gln Leu Pro Val Met Val Ile Val Thr Pro Gln Xaa Arg Lys Asn Ser
```

105

Val Trp Thr Gln Asp Gly Pro Ser Ala Gln Ile Leu Gln Gln Leu Val 125 120 Val Leu Ala Ala Glu Xaa Leu Pro Met Leu Xaa Xaa Gln Leu Met Asp 135 140 Pro Arg Gly Pro Gly Asp Ile Arg Thr Xaa Phe Arg Pro Pro Leu Asp 155 150 Ile Tyr Asp Val Leu Ile Arg Leu Ser Pro Arg His Ile Pro Arg His 170 165 Arg Gln Ala Val Asp Ser Pro Ala Ala Ser Phe Cys Arg Gly Leu Leu 180 185 Ser Gln Pro Gly Pro Ser Ser Leu Met Pro Val Leu Gly Xaa Asp Pro 205 200 195 Pro Gln Leu Tyr Leu Thr Gln Leu Xaa Glu Ala Phe Gly Asp Leu Ala 215 220 Leu Phe Phe Tyr Asp Gln His Gly Gly Glu Val Ile Gly Val Leu Trp 235 230 Lys Pro Thr Ser Phe Gln Pro Gln Pro Phe Lys Ala Ser Ser Thr Lys 245 250 Gly Arg Met Val Met Ser Arg Gly Glu Leu Val Met Val Pro Asn 260 265 Val Glu Ala Ile Leu Glu Asp Phe Ala Val Leu Gly Glu Gly Leu Val 275 280 Gln Thr Val Glu Ala Arg Ser Glu Arg Trp Thr Val 295 290

<210> 420 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 420

Met Gly Gly Ile Trp Asn Ala Leu Ser Met Ser Ser Phe Ser Phe His
-15 -10 -5

Ser Ser Ser Cys Ser Ala Leu Ser Ala Lys Ser Leu Leu Ser Arg His
1 5 10

His Ile Leu Gln Gln Phe Leu Val Arg Lys Ser Val Pro Leu Glu Asn
15 20 25

Ala Ser Leu Pro Phe Pro His Leu Gly Ser Ser Leu Phe Lys Ile Val
30 35 40 40 45

<210> 421 <211> 57 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -30..-1

Met Pro Thr Gly Lys Gln Leu Ala Asp Ile Gly Tyr Lys Thr Phe Ser
-30 -25 -20 -15
Thr Ser Met Met Leu Leu Thr Val Tyr Gly Gly Tyr Leu Cys Ser Val

-10 -5 Arg Val Tyr His Tyr Phe Gln Trp Arg Arg Ala Gln Arg Gln Ala Ala 5 10 Glu Glu Gln Lys Xaa Ser Gly Ile Met <210> 422 <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -17..-1 <400> 422 Met Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val -10 Gly Phe Pro Val Ser Gln Asp Gln Glu Arg Glu Lys Arg Ser Ile Ser 10 Asp Ser Asp Glu Leu Ala Ser Gly Xaa Phe Val Phe Pro Tyr Pro Tyr 20 25 Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe 40 Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro Leu Pro Ser Glu Lys 65 <210> 423 <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -17..-1 Met Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val -15 -10 Gly Phe Pro Val Ser Gln Asp Xaa Glu Arg Glu Lys Arg Ser Ile Ser 10 Asp Ser Asp Glu Leu Ala Ser Gly Phe Phe Val Phe Pro Tyr Pro Tyr 20 25 Pro Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe 40 Arg Arg Asn Phe Pro Ile Pro Ile Pro Glu Ser Ala Pro Thr Thr Pro 50 55 Leu Pro Ser Glu Lys 65

<210> 424 <211> 69 <212> PRT

<213> Homo sapiens

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<221> SIGNAL
<222> -29..-1
<400> 424
Met Thr Cys Arg Gly Ser Cys Ser Tyr Ala Thr Arg Arg Ser Pro Ser
                             -20
           -25
Glu Leu Ser Leu Leu Pro Ser Ser Leu Trp Val Leu Ala Thr Ser Ser
      -10 -5
Pro Thr Ile Thr Ile Ala Leu Ala Met Ala Ala Gly Asn Leu Cys Pro
                      15
 5 10
Leu Pro Ser Ser Xaa Arg Xaa Lys Arg Arg Trp Cys Gln Ala Xaa Gln
                          30
20 25
Gln Xaa Ala Leu Leu
            4.0
<210> 425
<211> 122
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
<400> 425
Met Val Pro Trp Pro Arg Gly Lys Val Lys Thr Ala Pro Ile Pro Ile
  -55 +50
                          -45
Ser Arg Phe Pro Phe Leu Pro Thr His Asp Pro Pro Thr Pro Ala His
-40 -35
                                -30
Trp Ser Pro Ala Ser His Gln Gln Phe Lys His Xaa Ser Pro Leu Leu
                             -15 -10
           -20
Thr Leu Ala Leu Leu Gly Gln Cys Ser Leu Phe Xaa Asn Leu Arg Lys
                         1
       - 5
Lys Leu Ala Gly Gln Lys Ala Lys Lys Leu Pro Ser Phe Ser Ser Leu
                            20
 10 15
Pro Leu Thr Leu Trp Pro Leu Thr Pro Gln Phe Ala Glu Leu Thr Thr
                                35
    30
Val Ala Gln Lys Lys Leu Arg Trp Ser Gly Thr Leu Gly Trp Gly Pro
                 50
          45
Val Pro Ser Trp Val Gln Phe Phe Leu Gly
         60
<210> 426
<211> 41
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Arg Cys Ser Gly Ser Pro Leu Pro Leu
5 10

<210> 427
<211> 50
<212> PRT
<213> Homo sapiens

<220>
<221> SIGNAL
<222> -36..-1

<400> 427
Met Ala Pro His Thr Ala Ser Phe Gly Val Cys Pro Leu Leu Ser Val

-35 -30 -25
Thr Arg Val Val Ala Thr Glu His Trp Leu Phe Leu Ala Ser Leu Ser
-20 -15 -10 -5

Gly Ile Lys Thr Tyr Gln Ser Tyr Ile Ser Val Phe Cys Lys Val Thr
1 5 10

Leu Ile

<210> 428 <211> 136 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 428

<222> -18..-1

Met Asp Ser Leu Arg Lys Met Leu Ile Ser Val Ala Met Leu Gly Ala
-15 -10 -5

Xaa Ala Gly Val Gly Tyr Ala Leu Leu Val Ile Val Thr Pro Gly Glu
1 5 10

Ser Arg Glu Glu Ala Ala Arg Thr Gln Gln Leu Leu Ala Thr Leu 35 40 45

Gln Glu Ala Ala Thr Thr Gln Glu Asn Val Ala Trp Arg Lys Asn Trp 50 55 60

Met Val Gly Glu Gly Gly Ala Thr Gly Xaa His Arg Glu Thr Gly
65 70 75

Leu Ala Ser Val Gly Ala Gly Pro Trp Leu Gly Arg Arg Asn Pro Arg 80 85 90

Gln Leu Ser Pro Ser Trp Ala Xaa Arg Lys Ile Arg Xaa Glu Asn Xaa 95 100 105 110

Met Pro Gly Leu Ser Gly Val Leu

115

<210> 429 <211> 194 <212> PRT <213> Homo sapiens

<220>

<221> SIGNAL <222> -65..-1

Met Gln Asp Ala Pro Leu Ser Cys Leu Ser Pro Thr Lys Trp Ser Ser -55 -60 Val Ser Ser Ala Asp Ser Thr Glu Lys Ser Ala Ser Ala Ala Gly Thr -40 - 45 Arg Asn Leu Pro Phe Gln Phe Cys Leu Arg Gln Ala Leu Arg Met Lys -25 -30 Ala Ala Gly Ile Leu Thr Leu Ile Gly Cys Leu Val Thr Gly Val Glu -10 -15 Ser Lys Ile Tyr Thr Arg Cys Lys Leu Ala Lys Ile Phe Ser Arg Ala 10 Gly Leu Asp Asn Xaa Arg Gly Phe Ser Leu Gly Asn Trp Ile Cys Met 25 20 Ala Tyr Tyr Glu Ser Gly Tyr Asn Thr Thr Ala Gln Thr Val Leu Asp 40 Asp Gly Ser Ile Asp Tyr Gly Ile Phe Gln Ile Asn Ser Phe Ala Trp 5.5 Cys Arg Arg Gly Lys Leu Lys Glu Asn Asn His Cys His Val Ala Cys 70 Ser Ala Leu Xaa Thr Asp Asp Leu Thr Asp Ala Ile Ile Cys Ala Xaa 8.5 Lys Ile Val Lys Glu Thr Gln Gly Met Asn Tyr Trp Gln Gly Trp Lys 105 100 Lys His Cys Glu Gly Arg Asp Leu Ser Xaa Trp Lys Lys Gly Cys Glu 120 115 Val Ser

<210> 430 <211> 141 <212> PRT <213> Homo sapiens

<221> SIGNAL <222> -69..-1

<400> 430

<220>

Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser -65 Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln -45 -50 Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Ile Lys Val Ile -25 -30 -35 Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile -10 -15 Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Val Xaa 20 Lys Xaa Ser Glu Glu Gly Arg Met Gly Gln Xaa Gly Glu Glu Xaa Xaa Asn Ser Leu Asn Phe Pro Xaa Ala Ser Leu Leu Xaa Leu Ile Cys Gln 50 Xaa Gln Gly Phe Asn Gly Glu Ser Cys Ser Pro Val Gly

<400> 432

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<210> 431
<211> 248
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -69..-1
<400> 431
Met Thr Ser Gln Pro Val Pro Asn Glu Thr Ile Ile Val Leu Pro Ser
            -65
                              -60
Asn Val Ile Asn Phe Ser Gln Ala Glu Lys Pro Glu Pro Thr Asn Gln
          -50
                 -45
Gly Gln Asp Ser Leu Lys Lys His Leu His Ala Glu Xaa Lys Val Ile
     -35 √ -30
                               -25
Gly Thr Ile Gln Ile Leu Cys Gly Met Met Val Leu Ser Leu Gly Ile
                 -15
                           -10
Ile Leu Ala Ser Ala Ser Phe Ser Pro Asn Phe Thr Gln Val Thr Ser
              1
                           5
Thr Leu Leu Asn Ser Ala Tyr Pro Phe Ile Gly Pro Phe Phe Ile
                          20
Ile Ser Gly Ser Leu Ser Ile Ala Thr Lys Lys Arg Leu Thr Asn Leu
 30
                       35
Leu Val His Thr Thr Leu Val Gly Ser Ile Leu Ser Ala Leu Ser Ala
                   50
Leu Val Gly Phe Ile Xaa Leu Ser Val Lys Gln Ala Thr Leu Asn Pro
                65
                        70 . 75
Ala Ser Leu Xaa Cys Glu Leu Xaa Lys Asn Asn Ile Pro Thr Xaa Xaa
                       85
Tyr Val Xaa Tyr Phe Tyr His Asp Ser Leu Tyr Thr Thr Asp Xaa Tyr
                          100
Thr Ala Lys Ala Xaa Leu Ala Gly Thr Leu Ser Leu Met Leu Ile Cys
                       115
                              120
Thr Leu Leu Glu Phe Cys Xaa Xaa Val Leu Thr Ala Val Leu Arg Trp
 125 130
                           135
Lys Gln Ala Tyr Ser Asp Phe Pro Gly Ser Val Leu Phe Leu Pro Xaa
140 145 150 155
Ser Tyr Ile Gly Asn Ser Gly Met Ser Ser Lys Met Thr His Asp Cys
             160
                             165 170
Gly Tyr Glu Glu Leu Leu Thr Ser
         175
<210> 432
<211> 49
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -36..-1
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Phe

<210> 433 <211> 86 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1 Met Val Ala Leu Asn Leu Ile Leu Val Pro Cys Cys Ala Ala Trp Cys -10 - 5 Asp Pro Arg Arg Ile His Ser Gln Asp Asp Val Leu Arg Ser Ser Ala 10 Ala Asp Thr Gly Ser Ala Met Gln Arg Arg Glu Ala Trp Ala Gly Trp 25 Arg Arg Ser Gln Pro Phe Ser Val Gly Leu Pro Ser Ala Glu Arg Leu 40 45 Glu Asn Gln Pro Gly Lys Leu Ser Trp Arg Ser Leu Val Gly Glu Gly 60 55 His Arg Ile Cys Asp Leu 70

<210> 434 <211> 144 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -58..-1

<400> 434 Met Thr Arg Leu Cys Leu Pro Arg Pro Glu Ala Arg Glu Asp Pro Ile -55 -50 -45 Pro Val Pro Pro Arg Gly Leu Gly Ala Gly Glu Gly Ser Gly Ser Pro -35 Val Arg Pro Pro Val Ser Thr Trp Gly Pro Ser Trp Ala Gln Leu Leu -25 -20 -15 Asp Ser Val Leu Trp Leu Gly Ala Leu Gly Leu Thr Ile Gln Ala Val -5 Phe Ser Thr Thr Gly Pro Ala Leu Leu Leu Leu Leu Val Ser Phe Leu 10 15 Thr Phe Asp Leu Leu His Arg Pro Ala Val Thr Leu Cys His Ser Ala 25 30 Asn Phe Ser Pro Gly Ala Arg Val Arg Gly Pro Val Lys Val Leu Asp 45 Ser Arg Arg Leu Tyr Ser Cys Lys Trp Val Gln Ser Gln Asp Asn Leu 65 60 Ala Ser Arg Lys His Cys Cys Cys Cys Ser Trp Gly Trp Ala Arg Ser

80

<210> 435 <211> 121

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<212> PRT
  <213> Homo sapiens
  <220>
  <221> SIGNAL
  <222> -16..-1
  <400> 435
  Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
     -15 -10
  Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
                                   10
  Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
          20
                            25
  Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Ser
                           40
                                             45
  Glu Ser Pro Pro Gly Arg Gly Xaa Val Pro Xaa Ala Gly Glu Xaa Pro
                       55
  Val Pro Pro Pro Leu Xaa Asp Leu Xaa Met Thr Pro Arg Xaa Xaa Arg
                   70
                                   75
. Ala Trp Gly Pro Val Gly Pro Lys Val Pro Pro Ala Val Ser Pro Ala
               85
                     90
  Leu Gly Ser Gly Glu His Pro Xaa Xaa
  <210> 436
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<211> 162
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -16..-1
<400> 436
Met Glu Arg Leu Val Leu Thr Leu Cys Thr Leu Pro Leu Ala Val Ala
                     -10
Ser Ala Gly Cys Ala Thr Thr Pro Ala Arg Asn Leu Ser Cys Tyr Gln
                                10
Cys Phe Lys Val Ser Ser Trp Thr Glu Cys Pro Pro Thr Trp Cys Ser
                          25
Pro Leu Asp Gln Val Cys Ile Ser Asn Glu Val Val Val Ser Phe Lys
                        4.0
Trp Ser Val Arg Val Leu Leu Ser Lys Arg Cys Ala Pro Arg Cys Pro
                     55
                                        60
Asn Asp Asn Met Xaa Phe Glu Trp Ser Pro Ala Pro Met Val Gln Gly
                 70
                                    75 80
Val Ile Thr Arg Arg Cys Cys Ser Trp Ala Leu Cys Asn Arg Ala Leu
                                 90
Thr Pro Gln Glu Gly Arg Trp Ala Leu Xaa Gly Gly Leu Leu Gln
          100
                            105
Asp Pro Ser Arg Gly Xaa Lys Thr Trp Val Arg Pro Gln Leu Gly Leu
                         120
                              125
Pro Leu Cys Leu Pro Xaa Ser Asn Pro Leu Cys Pro Xaa Glu Thr Gln
        135
Glu Gly
145
```

<210> 437 <211> 110 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -20..-1 Met Xaa Leu Met Val Leu Val Phe Thr Ile Gly Leu Thr Leu Leu Leu -10 -15 Glv Xaa Gln Ala Met Pro Ala Asn Arg Leu Ser Cys Tyr Arg Lys Ile 1 Leu Lys Asp His Asn Cys His Asn Leu Pro Glu Gly Val Ala Asp Leu 20 Thr Gln Ile Asp Val Asn Val Gln Asp His Phe Trp Asp Gly Lys Gly 40 35 Cys Glu Met Ile Cys Tyr Cys Asn Phe Lys Arg Ile Ala Leu Leu Pro 50 Lys Arg Arg Phe Leu Trp Thr Lys Asp Leu Phe Arg Asp Ser Leu Gln 70 Gln Ser Met Arg Ile Phe Met Tyr Ser Gly Glu His His Ser 85 <210> 438

<210> 439 <211> 99 <212> PRT <213> Homo sapiens <220>

Gln Val Pro Arg Arg Ala Gly

<221> SIGNAL <222> -24..-1

<211> 71

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      Ser Leu Asn Thr
      Leu Leu Leu Leu Gly Gly Val Asn Lys Ile Ala Glu Lys

      -5
      1
      5

      Ile Cys Gly Asp Leu Lys Asp Pro Cys Lys Leu Asp Met Asn Phe Gly 10
      15
      20

      Ser Cys Tyr Glu Val His Phe Arg Tyr Phe Tyr Asn Arg Thr Ser Lys 30
      35
      40

      Arg Cys Glu Thr Phe Val Phe Ser Ser Cys Asn Gly Asn Leu Asn Asn 50
      55

      Phe Lys Leu Lys Ile Glu Arg Glu Val Xaa Cys Val Ala Lys Tyr Lys 60
      65
      70

      Pro Pro Arg 75
      75
```

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<210> 440
 <211> 169
 <212> PRT
 <213> Homo sapiens
<220>
 <221> SIGNAL
 <222> -25..-1
 <400> 440
 Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu
                   -20
                                      -15
 Leu Leu Pro Leu Ala Pro Ala Ala Ala Gln Asp Ser Thr Gln Ala Ser
            -5
                                  1
 Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Gln Arg Phe Phe Ala
       10
                          15
 Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala
                      30
 Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu
                                     50
 Asn His Gly Leu Val Pro Asp Gly Ala Val Cys Ser Asn Leu Pro Tyr
               60
                                  65
 Ala Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr His Tyr Arg Cys Ser
                             80
 Asn His Val Tyr Tyr Ala Lys Arg Val Leu Cys Ser Gln Pro Val Ser
 Ile Leu Ser Pro Asn Thr Leu Lys Glu Ile Glu Xaa Ser Ala Glu Val
           110
                            115
Ser Pro Thr Thr Asp Asp Leu Pro His Leu Thr Pro Leu His Ser Asp
           125
                                    130
Arg Thr Pro Asp Leu Pro Ala Leu Ala
              140
```

Ala Asp Cys Gly Thr Ile Leu Leu Gln Asp Lys Gln Arg Lys Ile Tyr -50 -55 Cys Val Ala Cys Gln Glu Leu Asp Ser Asp Val Asp Lys Asp Asn Pro -40 ~35 Ala Leu Asn Ala Gln Ala Ala Leu Ser Gln Ala Arg Glu His Gln Leu -20 Ala Ser Ala Ser Glu Leu Pro Leu Gly Ser Arg Pro Ala Pro Gln Pro - 5 Pro Val Pro Arg Pro Glu His Cys Glu Gly Ala Ala Ala Gly Leu Lys 10 15 Ala Ala Gln Gly Pro Pro Ala Pro Ala Val Pro Pro Asn Thr Xaa Val 30 25 Met Ala Cys Thr Gln Thr Ala Leu Leu Gln Lys Leu Thr Trp Ala Ser 45 Ala Glu Leu Gly Ser Xaa Thr Ser Xaa Gly Lys Xaa Ala Ser Ser Cys 60 65 Val Ala Leu Ser Ala His Val Arg Arg Pro Cys Ala Ala Cys Ser Ser 75 Tyr Ser Thr Lys Arg Ser Pro

<210> 442 <211> 70 <212> PRT <213> Homo sapiens

<220>
<221> SIGNAL
<222> -15..-1

<400> 442

Met Ile Leu Cys Phe Leu Leu Pro His His Arg Leu Gln Glu Ala Arg
-15 -10 -5 -5 -1

Gln Ile Gln Val Leu Lys Met Leu Pro Arg Glu Lys Leu Arg Arg Arg
5 10 15 -5

Glu Glu Arg Lys Gln Ile Asn Gly Lys Lys Xaa Arg Thr Lys Tyr Glu
20 25 -30

Thr Pro Arg Lys Xaa Xaa Gly Lys Lys Gly Gly Asn Xaa Xaa Xaa Xaa
35 40 45

Xaa Leu Ser Lys Arg Asp

<210> 443 <211> 381 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -33..-1

<400> 443

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Lys Met Ala Thr Val Lys Ser Glu Leu Ile Glu Arg Phe Thr Ser Glu
                          25
 Lys Pro Val His His Ser Lys Val Ser Ile Ile Gly Thr Gly Ser Val
             4 0
 Gly Met Ala Cys Ala Ile Ser Ile Leu Leu Lys Gly Leu Ser Asp Glu
           55 60
 Leu Ala Leu Val Asp Leu Asp Glu Xaa Lys Leu Lys Gly Glu Thr Met
        70
                      75
 Asp Leu Gln His Gly Ser Pro Phe Thr Lys Met Pro Asn Ile Val Cys
                   90
 80 85
 Ser Lys Xaa Tyr Phe Val Thr Ala Asn Ser Asn Leu Val Ile Ile Thr
           100 105 110
 Ala Gly Ala Arg Gln Xaa Lys Gly Glu Thr Arg Leu Asn Leu Xaa Gln
         115 120 125
 Arg Asn Val Ala Ile Phe Lys Leu Met Ile Ser Ser Ile Val Gln Tyr
                         140
    130 135
 Ser Pro His Cys Lys Leu Ile Ile Val Ser Asn Pro Val Asp Ile Leu
   145 150 155
 Thr Tyr Val Ala Trp Lys Leu Ser Ala Phe Pro Lys Asn Arg Ile Ile
    165 170 175
. Gly Ser Gly Cys Asn Leu Ile Xaa Ala Arg Phe Arg Phe Leu Ile Gly
           180 185 190
 Gln Lys Leu Gly Ile His Ser Glu Ser Cys His Gly Trp Ile Leu Gly
         195 200
 Glu His Gly Asp Ser Ser Val Pro Val Trp Ser Gly Val Asn Ile Ala
                                   220
      210 215
 Gly Val Pro Leu Lys Asp Leu Asn Ser Asp Ile Gly Thr Asp Lys Asp
    225 230
                                235
 Pro Glu Gln Trp Lys Asn Val His Lys Glu Val Thr Ala Thr Ala Tyr
                   250 255
    245
 Glu Ile Ile Lys Met Lys Gly Tyr Thr Ser Trp Ala Ile Gly Leu Ser
           260 265 270
 Val Ala Asp Leu Thr Glu Ser Ile Leu Lys Asn Leu Arg Arg Ile His
         275
                       280 285
 Pro Val Ser Thr Ile Thr Lys Gly Leu Tyr Gly Ile Xaa Glu Glu Val
                    295 300
 Phe Leu Ser Ile Pro Cys Ile Leu Gly Glu Asn Gly Ile Thr Asn Leu
   305 310 315
 Ile Lys Ile Lys Leu Thr Pro Glu Glu Glu Ala His Leu Lys Lys Ser
 320 325
                             330
 Ala Lys Thr Leu Trp Glu Ile Gln Asn Lys Leu Lys Leu
           340
```

<210> 445

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<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 445
Met Val Leu Thr Thr Leu Pro Leu Pro Ser Ala Asn Ser Pro Val Asn
                       -30
Met Pro Thr Thr Gly Pro Asn Ser Leu Ser Tyr Ala Ser Ser Ala Leu
 -20 -15
                             -10
Ser Pro Cys Leu Thr Ala Pro Lys Ser Pro Arg Leu Ala Met Met Pro
                           5
Asp Asn
<210> 446
<211> 51
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> ~26..-1
<400> 446
Met Thr Pro Trp Cys Leu Ala Cys Leu Gly Arg Arg Pro Leu Ala Ser
                                    -15
  -25 -20
Leu Gln Trp Ser Leu Thr Leu Ala Trp Cys Gly Ser Gly Ser His Trp
-10 -5
                      1
Thr Glu Arg Pro Xaa Gln Xaa Ser Pro Trp Xaa Ser Leu Ser Ala Thr
                     15
Thr Arg Gly
     25
<210> 447
<211> 242
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -30..-1
<400> 447
Met Gly Glu Ala Ser Pro Pro Ala Pro Ala Arg Arg His Leu Leu Val
-30 -25 -20 -15
Leu Leu Leu Leu Ser Thr Leu Val Ile Pro Ser Ala Ala Ala Pro
             -10
                            ~ 5
Ile His Asp Ala Asp Ala Gln Glu Ser Ser Leu Gly Leu Thr Gly Leu
                    10
Gln Ser Leu Leu Gln Gly Phe Ser Arg Leu Phe Leu Lys Gly Asn Leu
                    25
Leu Arg Gly Ile Asp Ser Leu Phe Ser Ala Pro Met Asp Phe Arg Gly
```

40 45 Leu Pro Gly Asn Tyr His Lys Glu Glu Asn Gln Glu His Gln Leu Gly 60 Asn Asn Thr Leu Ser Ser His Leu Gln Ile Asp Lys Met Thr Asp Asn 75 Lys Thr Gly Glu Val Leu Ile Ser Glu Asn Val Val Ala Ser Ile Gln 90 Pro Xaa Glu Gly Xaa Phe Glu Gly Asp Leu Lys Val Pro Arg Met Glu 105 110 Glu Lys Glu Ala Leu Val Pro Xaa Gln Lys Ala Thr Asp Ser Phe His 120 125 Thr Glu Leu His Pro Arg Val Ala Phe Trp Ile Ile Lys Leu Pro Arg 135 140 Arg Arg Ser His Gln Asp Ala Leu Glu Gly Gly His Trp Leu Xaa Glu 150 155 Lys Arg His Arg Leu Gln Ala Ile Arg Asp Gly Leu Arg Lys Gly Thr 170 His Lys Asp Xaa Leu Xaa Xaa Gly Thr Glu Ser Ser His Ser Arg 185 190 Leu Ser Pro Arg Lys Xaa His Leu Leu Tyr Ile Leu Xaa Pro Ser Arg 195 200 Gln Leu

<210> 448 <211> 154 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -60..-1

Met Gly Ser Lys Cys Cys Lys Gly Gly Pro Asp Glu Asp Ala Val Glu
-60 -55 -50 -50

Arg Gln Arg Arg Gln Lys Leu Leu Leu Ala Gln Leu His His Arg Lys
-40 -35 -30

Arg Val Lys Ala Ala Gly Gln Ile Gln Ala Trp Trp Arg Gly Val Leu
-25
-20
-15

Val Arg Arg Thr Leu Leu Val Ala Ala Leu Arg Ala Trp Met Ile Gln
-10 -5 1

Cys Trp Trp Arg Thr Leu Val Gln Arg Arg Ile Arg Gln Arg Arg Gln 5 10 15 20 Ala Leu Leu Gly Val Tyr Val Ile Gln Glu Gln Ala Ala Val Lys Leu

Ala Leu Leu Gly Val Tyr Val Ile Gln Glu Gln Ala Ala Val Lys Leu
25 30 35

Gln Ser Cys Ile Arg Met Trp Gln Cys Arg Gln Cys Tyr Arg Gln Met
40 45 50

Cys Asn Ala Leu Cys Leu Phe Gln Val Pro Lys Ser Ser Leu Ala Phe 55 60 65

Gln Thr Asp Gly Phe Leu Gln Val Gln Tyr Ala Ile Pro Ser Lys Gln 70 75 80

Pro Glu Phe His Ile Glu Ile Leu Ser Ile

<210> 449

<211> 89

<212> PRT

<213> Homo sapiens

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<220>
<221> SIGNAL
<222> -61..-1
<400> 449
Met Asn Ala Ala Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr
                                     -50
                     -55
Glu Thr Glu Val Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro
                                   - 35
                -40
Glu Ala Arg Ser His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala
                                -20
              -25
Leu Leu Pro Cys Asn Leu His Cys Ser Trp Leu His Ser Ser Pro Arg
                                    1
                   -5
        -10
Pro Asp Pro His Ser His Phe Pro Ser Xaa Arg Arg Cys Pro Leu Pro
              10
His Pro Cys Ala Thr Tyr Pro Pro Xaa
               25
```

30

Phe Asp Leu Asp Met Asp His Thr Ile

20

<210> 450

<210> 452 <211> 121 <212> PRT

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<213> Homo sapiens
<220>
<221> SIGNAL
<222> -38..-1
<400> 452
Met Glu Ser Pro Gln Leu His Cys Ile Leu Asn Ser Asn Ser Val Ala
    -35 -30 -25
Cys Ser Phe Ala Val Gly Ala Gly Phe Leu Ala Phe Leu Ser Cys Leu
 -20 - -15
                          -10
Ala Phe Leu Val Leu Asp Thr Gln Glu Thr Arg Ile Ala Gly Thr Arg
 -5 1 5
Phe Lys Thr Ala Phe Gln Leu Leu Asp Phe Ile Leu Ala Val Leu Trp
    15 20
Ala Val Val Trp Phe Met Gly Phe Cys Phe Leu Ala Asn Gln Trp Gln
  30 35
His Ser Pro Pro Lys Glu Xaa Leu Leu Gly Ser Ser Ser Ala Gln Ala
 45 50
Ala Ile Gly Xaa His Leu Leu His Pro Cys Leu Asp Ile Pro Xaa
 60 65
Leu Pro Gly Xaa Pro Gly Pro Pro Lys
               80
<210> 453
<211> 166
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
<400> 453
Met Ser Thr Val Gly Leu Phe His Phe Pro Thr Pro Leu Thr Arg Ile
                     -30
Cys Pro Ala Pro Trp Gly Leu Arg Leu Trp Glu Lys Leu Thr Leu Leu
 -20 -15
                                -10
Ser Pro Gly Ile Ala Val Thr Pro Val Gln Met Ala Gly Lys Lys Asp
          1 5
Tyr Pro Ala Leu Leu Ser Leu Asp Glu Asn Glu Leu Glu Glu Gln Phe
                      20 25
Val Lys Gly His Gly Pro Gly Gly Gln Ala Thr Asn Lys Thr Ser Asn
                    35
Cys Val Val Leu Lys Xaa Ile Pro Ser Gly Ile Val Val Lys Cys His
                 50
Gln Thr Arg Ser Val Asp Gln Asn Arg Lys Leu Ala Arg Lys Ile Leu
              65
                              70
Gln Glu Lys Val Xaa Val Phe Tyr Asn Gly Glu Asn Ser Pro Val His
                           85 90
Lys Glu Lys Arg Glu Ala Ala Lys Lys Gln Glu Arg Lys Lys Arg
    95 100
                             105
Ala Lys Glu Thr Leu Glu Lys Lys Xaa Leu Leu Lys Xaa Leu Trp Glu
     110
                                     120
```

Ser Ser Lys Lys Val His 125 <210> 454 <211> 180 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -26..-1 <400> 454 Met Gly Ile Gln Thr Ser Pro Val Leu Leu Ala Ser Leu Gly Val Gly -25 -20 -15 Leu Val Thr Leu Leu Gly Leu Ala Val Gly Ser Tyr Leu Val Arg Arg - 5 Ser Arg Arg Pro Gln Val Thr Leu Leu Asp Pro Asn Glu Lys Tyr Leu 10 15 Leu Arg Leu Leu Asp Lys Thr Thr Val Ser His Asn Thr Lys Arg Phe 30 Arg Phe Ala Leu Pro Thr Ala His His Thr Leu Gly Leu Pro Val Gly 45 Lys His Ile Tyr Leu Ser Thr Arg Ile Asp Gly Ser Leu Val Ile Arg 60 65 Pro Tyr Thr Pro Val Thr Ser Asp Glu Asp Gln Gly Tyr Val Asp Leu 8.0 Val Xaa Lys Val Tyr Leu Lys Gly Val His Pro Lys Phe Pro Glu Gly 90 95 Gly Lys Met Ser Xaa Tyr Leu Asp Xaa Leu Lys Val Gly Asp Xaa Val 110 Glu Phe Xaa Gly Pro Ser Gly Leu Leu Thr Tyr Thr Gly Lys Gly His 125 130 Phe Asn Ile Gln Pro Asn Lys Asn Leu His Gln Asn Pro Glu Trp Arg 140 145 Arg Asn Trp Glu <210> 455 <211> 91 <212> PRT <213> Homo sapiens

<220> <221> SIGNAL <222> -64..-1 <400> 455 Met Thr Pro Arg Ile Leu Ser Glu Val Gln Phe Ser Ala Phe Cys Pro -60 -55 Tyr Trp Thr Ile Ala Arg Ile Leu Glu Arg Val Gly Ser Ala Cys Phe -45 -40 - 35 Arg Leu Glu Leu Cys Ala Ala Ile Val Gly Tyr Phe Val Leu Asp Val -25 -20 Arg Thr Phe Leu Phe Ile Val Val Cys Val Ile Cys Val Thr Leu Asn -10 - 5 Phe Pro Arg Phe Tyr Phe Leu Cys Leu Ser Ser Leu Thr Ala Phe Gly 10 Thr Pro Pro Ile Gly Val His Ile Pro Ser Pro

2.0

25

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<210> 456
<211> 257
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -23..-1
<400> 456
Met Arg Arg Ile Ser Leu Thr Ser Ser Pro Val Arg Leu Leu Leu Xaa
   -20 -15 -10
Leu Leu Leu Leu Ile Ala Leu Glu Ile Met Val Gly Gly His Ser
 - 5
                    1
Leu Cys Phe Asn Phe Thr Ile Lys Ser Leu Ser Arg Pro Gly Gln Pro
10 15 20
Trp Cys Glu Ala His Val Phe Leu Asn Lys Asn Leu Phe Leu Gln Tyr
      30
                35 40
Asn Ser Asp Asn Asn Met Val Lys Pro Leu Gly Leu Leu Gly Lys Lys
                       50
       4.5
Val Tyr Ala Thr Ser Thr Trp Gly Glu Leu Thr Gln Thr Leu Gly Glu
                    65
Val Gly Arg Asp Leu Arg Met Leu Leu Cys Asp Ile Lys Pro Gln Ile
                 80
Lys Thr Ser Asp Pro Ser Thr Leu Gln Val Xaa Xaa Phe Cys Gln Arg
              95
                  100 105
Glu Ala Glu Arg Cys Thr Gly Ala Ser Trp Gln Phe Ala Thr Asn Gly
           110 115 120
Glu Lys Ser Leu Leu Phe Asp Ala Met Asn Met Thr Trp Thr Val Ile
       125
                      130 135
Asn His Glu Ala Ser Xaa Ile Lys Glu Thr Trp Lys Lys Asp Arg Xaa
                    145 150
Leu Glu Xaa Tyr Phe Arg Lys Leu Ser Lys Gly Asp Cys Asp His Trp
                160 165
Leu Arg Glu Phe Leu Gly His Trp Glu Ala Met Pro Xaa Pro Xaa Val
   175 180 185
Ser Pro Xaa Asn Ala Ser Xaa Ile His Trp Ser Ser Ser Xaa Leu Pro
      190 195 200
Xaa Xaa Trp Ile Ile Leu Gly Ala Phe Ile Leu Leu Xaa Leu Met Gly
      205 210 215
Ile Val Leu Ile Cys Val Trp Trp Gln Asn Gly Xaa Xaa Ser Thr Xaa
                   225
Xaa
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-50

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<210> 457
<211> 193
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -60..-1
<400> 457
Met Cys Pro Ser Leu Glu Glu Ala Pro Ser Val Lys Gly Thr Leu Pro
                  -55
```

Cys Ser Gly Gln Gln Pro Phe Pro Phe Gly Ala Ser Asn Ile Pro -35 Leu Leu Gly Arg Ser Arg Lys Val Ala Arg Gly Ala Pro Val Leu -20 -25 Trp Pro Phe Leu Thr Trp Ile Asn Pro Ala Leu Ser Ile Cys Asp Pro -- 5 Leu Gly Ser Cys Gly Trp Xaa Cys His Thr Ala Gln Val Pro Ala Pro 10 1.5 Leu Gln Leu Pro Thr Ala Cys Pro Pro Leu Pro His Gly Thr Arg Ala 30 25 Val Gly Pro Thr Pro Gly Leu Leu Pro Glu Ala Ala Pro Xaa Thr 45 Xaa Gly Ala Leu Ser Ser Arg Ser Arg His Trp Ser Cys Ser Ile Val 60 Xaa Cys Leu His Leu His Xaa Leu Leu Ser Val Glu Thr Arg Xaa Phe 75 80 Xaa Lys His Leu Leu Val Leu Val Ala Val Ala His Ser Val Leu 90 95 Glu Pro Pro Ala Leu Val Pro Asn Val Gln Cys Glu Met Cys Thr His 110 Ser Gly Pro Arg Asp Leu Glu Ala Ala Val Val Ser Pro Ala Pro Trp 125 Glu

<210> 458 <211> 107 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -28..-1

<210> 459 <211> 121 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1

<400> 459 Met Leu Val Leu Arg Ser Ala Leu Thr Arg Ala Leu Ala Ser Arg Thr -10 -5 . 1 Leu Ala Pro Gln Met Cys Ser Ser Phe Ala Thr Gly Pro Arg Gln Tyr 5 10 . 15 Asp Gly Ile Phe Tyr Glu Phe Arg Ser Tyr Tyr Leu Lys Pro Ser Lys 25 30 35 Met Asn Glu Phe Leu Glu Asn Phe Glu Lys Asn Ala Gln Leu Arg Thr 40 45 Ala His Ser Glu Leu Val Gly Tyr Trp Ser Val Xaa Phe Gly Gly Arg 60 Met Xaa Thr Val Phe His Ile Trp Lys Tyr Asp Asn Phe Ala His Arg 75 Thr Glu Phe Gln Lys Ala Leu Ala Lys Asp Lys Glu Trp Gln Glu Gln 85 90 Phe Leu Ile Pro Asn Leu Ala Leu Asn 100 . 105

<212> PRT <213 > Homo sapiens <220> <221> SIGNAL <222> -13..-1 Met Cys Leu Leu Thr Ala Leu Val Thr Gln Val Ile Ser Leu Arg Lys -5 -10 Asn Ala Glu Arg Thr Cys Leu Cys Lys Arg Arg Trp Pro Trp Xaa Pro 10 Ser Pro Arg Ile Tyr Cys Ser Ser Thr Pro Cys Asp Ser Lys Phe Pro 25 30 35 Thr Val Tyr Ser Ser Ala Pro Phe His Ala Pro Leu Pro Val Gln Asn 40 4.5 Ser Leu Trp Gly His Pro Leu His Gly Cys Ser Trp Gln Cys His His 60 Pro Gln Gly Gln Asn Leu Gln Pro Ala Ser Leu Xaa Thr His Leu Ser 75 Lys Pro Lys Arg His Phe Xaa Lys Lys Xaa Cys Gln Ala

<210> 461 <211> 109

-332-

90 85 95

<210> 462 <211> 143 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -41..-1 <400> 462 Met Ala Thr Ala Thr Glu Gln Trp Val Leu Val Glu Met Val Gln Ala -35 Leu Tyr Glu Ala Pro Ala Tyr His Leu Ile Leu Glu Gly Ile Leu Ile -20 -15 Leu Trp Ile Ile Arg Leu Leu Phe Ser Lys Thr Tyr Lys Leu Gln Glu - 5 1 Arg Ser Asp Leu Thr Val Lys Glu Lys Glu Glu Leu Ile Glu Glu Trp 10 15 Gln Pro Glu Pro Leu Val Pro Pro Val Pro Lys Asp His Pro Ala Leu 30 35 Asn Tyr Asn Ile Val Ser Gly Pro Pro Ser His Lys Thr Val Val Asn 50 Gly Lys Glu Cys Ile Asn Phe Ala Ser Phe Asn Phe Leu Gly Leu Leu 65 Asp Asn Pro Arg Val Lys Ala Ala Ala Leu Ala Ser Leu Lys Lys Tyr 75 80 Gly Val Gly Thr Cys Gly Pro Cys Gly Phe Tyr Gly Thr Phe Glu 90 95

<210> 463

<211> 232

<212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL

<222> -30..-1

<400> 463

Met Ala Ala Thr Ser Gly Thr Asp Glu Pro Val Ser Gly Glu Leu Val -30 -25 -20 -15 Ser Val Ala His Ala Leu Ser Leu Pro Ala Glu Ser Tyr Gly Asn Xaa -10 - 5 Xaa Asp Ile Glu Met Ala Trp Ala Met Arg Ala Met Gln His Ala Glu 5 10 15 Val Tyr Tyr Lys Leu Ile Ser Ser Val Asp Pro Gln Phe Leu Lys Leu 20 25 Thr Lys Val Asp Asp Gln Ile Tyr Ser Glu Phe Arg Lys Asn Phe Glu 40 Thr Leu Arg Ile Asp Val Leu Xaa Pro Glu Xaa Leu Lys Ser Glu Ser 55 60 Ala Lys Glu Pro Pro Gly Tyr Asn Ser Leu Pro Leu Lys Leu Leu Gly 75 Thr Gly Lys Ala Ile Thr Lys Leu Phe Ile Ser Val Phe Arg Thr Lys 85 90 Lys Glu Arg Lys Glu Ser Thr Met Glu Glu Lys Lys Glu Leu Thr Val

```
100
                105
Glu Lys Lys Arg Thr Pro Arg Met Glu Glu Arg Lys Glu Leu Ile Val
115 120 125 130
Glu Lys Lys Lys Arg Lys Glu Ser Thr Glu Lys Thr Lys Leu Thr Lys
       135 140 145
Glu Glu Lys Lys Gly Lys Lys Leu Thr Lys Lys Ser Thr Lys Val Val
   150 155
Lys Lys Leu Cys Lys Val Tyr Arg Glu Gln His Ser Arg Ser Tyr Asp
 165 170 175
Ser Ile Glu Thr Thr Ser Thr Thr Val Leu Leu Ala Gln Thr Pro Leu
 180 185
Val Lys Cys Lys Phe Leu Tyr Asn
195 200
<210> 464
<211> 61
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 464
Met Thr Phe Arg His Gln Asp Asn Ser Leu Met Phe Phe Ser Met Met
 -20 -15 -10
Ala Thr Cys Thr Ser Asn Val Gly Phe Thr His Thr Thr Met Asn Cys
- 5
        1 5 10
Ser Leu Thr Ser Pro Val Asp Phe Lys Asp Leu Leu Arg Val Leu Leu
 15 20 25
Ile Lys Phe Gly Tyr Asp Arg Lys Ser Thr Ile Lys Ser
    30
            35
<210> 465
<211> 34
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -19..-1
<400> 465
Met Phe Leu Lys Ser Gly Ala Gly Leu Ser Ser Cys Leu Leu Pro Leu
       -15 -10 -5
Cys Trp Leu Glu Arg Lys Asp His Gly Arg Arg Pro Ser Xaa His Pro
       1 5
                         10
Gly Arg
  15
<210> 466
```

<211> 215 <212> PRT <213> Homo sapiens

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<221> SIGNAL
<222> -54..-1
<400> 466
Met Asn Xaa Tyr Ala Ser Pro Phe Asn Xaa Gln Leu Xaa Tyr Leu Xaa
              -50
                                 -45
Leu Ser Arg Phe Glu Cys Val His Arg Asp Gly Arg Val Ile Thr Leu
                          -30
          -35
Ser Tyr Gln Glu Gln Glu Leu Gln Asp Phe Leu Leu Ser Gln Met Ser
                                         -10
      -20
                      -15
Gln His Gln Val His Ala Val Gln Gln Leu Ala Lys Val Met Gly Trp
                   1
Gln Val Leu Ser Phe Ser Asn His Val Gly Leu Gly Pro Ile Glu Ser
           15
                                20
Xaa Gly Asn Ala Ser Ala Ile Thr Val Ala Pro Gln Val Val Thr Met
                             35
Leu Phe Gln Phe Val Met Asp Leu Lys Val Ala Ala Arg Leu Trp Phe
                         5.0
Ser Phe Leu Val Thr Asn Val Lys Thr Phe Gln Lys Val Met Phe Tyr
                                        70
                    65
Lys Ile Thr Asn Gly Val Ile Phe Val Gly His Ser Lys Lys Phe Ser
           80
                                    85
Gly Ile Lys Trp Lys Val Xaa Ile Leu Phe Ile Lys Trp Xaa Cys Leu
                                100
              9.5
Cys Leu His Leu Ala Leu Val Tyr Tyr Asp Phe Phe Gln Met Phe Pro
          110
                            115
Lys Xaa Val Ser Xaa Asn Phe Asp Leu Lys Cys Leu Gln Ile Asn Tyr
      125 130 135
Lys His Lys Glu Glu Ile Thr Ser Lys Arg Val Leu Phe Leu Lys Ile
Ile Ile Arg Lys Cys Phe Ile
<210> 467
<211> 27
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 467
Met Val Val His Leu Leu Tyr Ala His Leu Ser Phe Thr Ser Lys Arg
   -15 -10
Ala Val Val Met Leu Lys Leu Glu Ile Thr Phe
<210> 468
<211> 85
<212> PRT
<213> Homo sapiens
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<400> 468

<221> SIGNAL <222> -24..-1

<220>

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Met Cys Ser His Ala Ser Met Ser Phe His Thr Leu Phe His Leu Leu
      -20 -15 -10
Phe Leu Pro His Tyr Ile Glu Thr Phe Lys Pro Gln Ser Lys His Cys
                         5
 -5
Phe Phe Trp Ile Ala Ala Phe Leu Thr Ser Leu Leu Thr Pro Gln Ser
10
        15
                       20
Leu Gln Gly Phe His Ser Ser Leu Cys Ala Leu Arg Ser Gln His Phe
25 30
                   35
Pro Ser Thr Cys Asn Cys Phe Cys Tyr Leu Thr Ile Ile Ala Leu Xaa
     45
                50
Tyr Trp Asp Asn Leu
       60
```

<211> 51 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 469 Met Leu Arg Ile Ala Leu Thr Leu Ile Pro Ser Met Leu Ser Arg Ala **-1**5 -10 -5 Ala Gly Trp Cys Trp Tyr Lys Glu Pro Thr Gln Gln Phe Ser Tyr Leu 1 5 10 15 Cys Leu Pro Cys Leu Ser Trp Asn Lys Lys Gly Asn Val Leu Gln Leu 20 25 Pro Asn Phe 35

<213> Homo sapiens <220> <221> SIGNAL <222> -43..-1 <400> 470 Met Thr Pro Gln Tyr Leu Pro His Gly Gly Lys Tyr Gln Val Leu Gly -40 +35 Asp Tyr Ser Leu Ala Val Val Phe Pro Leu His Phe Ser Asp Leu Ile -25 -20 -15 Ser Val Leu Tyr Leu Ile Pro Lys Thr Leu Thr Thr Asn Thr Ala Val -10 -5 .. 1 Lys His Ser Ile Gln Lys Asn Cys Met Xaa Leu Val Leu Gly Lys Leu 10 15 Leu Ser Gln

<210> 471 <211> 63 <212> PRT <213> Homo sapiens

<210> 469

<210> 470 <211> 67 <212> PRT

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<220>
<221> SIGNAL
<222> ~15..-1
<400> 471
Met Gly Ile Leu Ser Thr Val Thr Ala Leu Thr Phe Ala Arg Ala Leu
         -10
                                - 5
Asp Gly Cys Arg Asn Gly Ile Ala His Pro Ala Ser Glu Lys His Arg
       5
                       10
                                          15
Leu Glu Lys Cys Arg Glu Leu Glu Ser Ser His Ser Ala Pro Gly Ser
 20 25
Thr Gln His Arg Arg Lys Thr Thr Arg Arg Asn Tyr Ser Ser Ala
<210> 472
<211> 179
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<212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -58..-1 <400> 472 Met Ser Thr Gly Gln Leu Tyr Arg Met Glu Asp Ile Gly Arg Phe His -55 -50 -45 Ser Gln Gln Pro Gly Ser Leu Thr Pro Ser Ser Pro Thr Val Gly Glu -40 -35 Ile Ile Tyr Asn Asn Thr Arg Asn Thr Leu Gly Trp Ile Gly Gly Ile -25 -20 -15 Leu Met Gly Ser Phe Gln Gly Thr Ile Ala Gly Gln Gly Thr Gly Ala -10 -5 1 5 Thr Ser Ile Ser Glu Leu Cys Lys Gly Gln Glu Leu Glu Pro Ser Gly 10 15 20 Ala Gly Leu Thr Val Ala Pro Pro Gln Ala Val Ser Leu Gln Gly Ile 25 30 35 Tyr Thr Leu Pro Trp Leu Leu Gln Leu Phe His Ser Thr Ala Leu Xaa 40 45 50 Xaa Xaa Gln Gln Pro Asn Gly Ser Leu Ser Leu Asn Ile Ser Ser Ser 55 60 65 70 His Ala Pro Xaa Pro Xaa Thr Cys Thr Leu Glu Pro Gly Val Asp Pro 75 80 85 Thr Arg Xaa Val Cys Ile Asn Pro His Pro Pro Pro Pro Ile Leu Lys 90 95 100 Xaa Pro Leu Ser Pro Tyr Pro Lys Pro Gln Leu Gly Thr His Ala Gly 105 110 Gln Val Asn 120

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<210> 473
<211> 238
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -71..-1
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<400> 473
Met Xaa Xaa Phe Thr Asp Pro Ser Ser Val Asn Glu Lys Lys Arg Arg
                       -65
Glu Arg Glu Glu Arg Gln Asn Ile Val Leu Trp Arg Gln Pro Leu Ile
                   -50
                                       -45
Thr Leu Gln Tyr Phe Ser Leu Glu Ile Leu Val Ile Leu Lys Glu Trp
               -35
Thr Ser Lys Leu Trp His Arg Gln Ser Ile Val Val Ser Phe Leu Leu
           -20
                               -15
Leu Leu Ala Gly Leu Ile Ala Thr Tyr Tyr Val Glu Gly Val His Gln
Gln Tyr Val Gln Arg Ile Glu Lys Gln Phe Leu Leu Tyr Ala Tyr Trp
                   15
Ile Gly Leu Gly Ile Leu Ser Ser Val Gly Leu Gly Thr Gly Leu His
               30
Thr Phe Leu Leu Tyr Leu Gly Pro His Ile Ala Ser Val Thr Leu Ala
                              50
Ala Tyr Glu Cys Asn Ser Val Asn Phe Pro Glu Pro Pro Tyr Pro Asp
Gln Ile Ile Cys Pro Asp Glu Glu Gly Thr Glu Gly Thr Ile Ser Leu
                       8.0
Trp Ser Ile Ile Ser Lys Val Arg Ile Glu Ala Cys Met Trp Gly Ile
                  95
                                      100
Gly Thr Ala Ile Gly Glu Leu Pro Pro Tyr Phe Met Ala Arg Ala Ala
              110 115
Arg Leu Ser Gly Ala Glu Pro Asp Asp Glu Glu Tyr Gln Glu Phe Glu
          125
                              130
Glu Met Leu Glu His Ala Glu Ser Ala Gln Val Arg Thr Val Gly Ile
                         145
Glu Asn Arg Thr Leu Tyr Phe Phe Leu Lys Arg Leu Leu Arg
                      160
```

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<210> 474
<211> 178
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -37..-1
Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln Phe
                            -30
Gln His Gln Gly Ala Val Glu Leu Leu Val Phe Asn Phe Leu Leu Ile
                        -15
Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg Phe Arg Phe
Leu His Glu Thr Gly Gly Ala Met Val Tyr Gly Leu Xaa Met Gly Leu
                                20
Ile Leu Xaa Tyr Ala Thr Ala Pro Thr Asp Ile Glu Ser Gly Xaa Val
                            35
Tyr Asp Cys Val Lys Leu Thr Phe Ser Pro Ser Thr Leu Leu Val Asn
                       5.0
Ile Thr Asp Gln Val Tyr Glu Tyr Lys Tyr Lys Arg Glu Ile Ser Gln
                   65
                                       70
His Xaa Ile Asn Pro His Xaa Gly Asn Ala Ile Leu Glu Lys Met Thr
               80
                                85
Phe Asp Pro Xaa Ile Phe Phe Asn Val Leu Leu Pro Pro Ile Ile Phe
```

```
105
         95
                         100
His Ala Gly Tyr Ser Leu Lys Lys Arg His Phe Phe Gln Asn Leu Gly
 110 115 120
Ser Ile Leu Thr Tyr Ala Phe Leu Gly Thr Ala Ile Ser Cys Ile Val
        130
Ile Gly
140
<210> 475
<211> 96
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 475
Met Ser Met Gln Phe Leu Phe Lys Met Val Ala Leu Cys Cys Cys Leu
 -20 -15
                                    -10
Trp Lys Ile Ser Gly Cys Glu Glu Val Pro Leu Thr Tyr Asn Leu Leu
- 5
             1
Lys Cys Leu Leu Asp Lys Ala His Cys Val Leu Leu Thr Pro Cys Gly
   15 20
Tyr Ile Phe Ser Leu Ile Ser Pro Glu Ile Leu Lys Leu Thr Leu Ile
             35
Thr Leu Xaa Ile Leu Leu Ile Leu Lys Asn Leu His Leu Leu Trp Leu
 45 50
Thr Val Ser Ser Xaa Cys Val His Arg Ser Ser Ala Arg Lys Glu Lys
                65
                                 70
<210> 476
<211> 41
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -24..-1
<400> 476
Met His Thr Phe Ala Asn Asp Arg Gly Leu Tyr Arg Ile Leu Leu Leu
          -20 -15 -10
His Phe Tyr Cys Leu Leu Arg Ser Ser Glu Tyr Ile Leu Gly Tyr Lys
             1
         -5
Val Leu Gly Val Phe Phe Pro Ile Leu
 10
                   15
<210> 477
<211> 113
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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<222> -27..-1

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<400> 477
Met Arg Xaa Lys Trp Lys Met Gly Gly Met Lys Tyr Ile Phe Ser Leu
   -25 -20
Leu Phe Phe Leu Leu Glu Gly Gly Xaa Thr Glu Gln Val Xaa His
 -10 -5
                        1
Ser Glu Thr Tyr Cys Met Phe Gln Asp Lys Lys Tyr Arg Val Gly Glu
                  15
         10
Arg Trp His Pro Tyr Leu Glu Pro Tyr Gly Leu Val Tyr Cys Val Asn
        25 30
Cys Ile Cys Ser Glu Asn Gly Asn Val Leu Cys Ser Arg Val Arg Cys
         4.5
Pro Asn Val His Cys Leu Ser Pro Val His Ile Pro His Leu Cys Cys
       60
Pro Arg Cys Pro Glu Asp Ser Leu Pro Pro Val Asn Asn Xaa Val Thr
    75
                    80
Ser
```

<210> 478 <211> 250 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -18..-1

<400> 478 Met Arg Ile Leu Gln Leu Ile Leu Leu Ala Leu Ala Thr Gly Leu Val -15 -10 -5 Gly Gly Glu Thr Arg Ile Ile Lys Gly Phe Glu Cys Lys Pro His Ser 1 5 10 Gln Pro Trp Gln Ala Ala Leu Phe Glu Lys Thr Arg Leu Leu Cys Gly 20 25 Ala Thr Leu Ile Ala Pro Arg Trp Leu Leu Thr Ala Ala His Cys Leu 35 40 Lys Pro Arg Tyr Ile Xaa His Leu Gly Gln His Asn Leu Gln Lys Glu 50 55 Glu Gly Cys Glu Gln Thr Arg Thr Ala Thr Glu Ser Phe Pro His Pro 70 Gly Phe Asn Asn Ser Leu Pro Asn Lys Asp Xaa Xaa Asn Asp Ile Met 85 90 Leu Val Xaa Met Xaa Ser Pro Val Ser Ile Thr Trp Ala Val Arg Pro 100 105 110 Leu Thr Leu Ser Ser Arg Cys Val Thr Ala Gly Thr Ser Cys Leu Ile 115 120 Ser Gly Trp Gly Ser Thr Ser Ser Pro Gln Leu Arg Leu Pro His Thr 130 135 Leu Arg Cys Ala Asn Ile Thr Ile Ile Glu His Gln Lys Cys Glu Asn 150 145 Ala Tyr Pro Gly Asn Ile Thr Asp Thr Met Val Cys Ala Ser Val Gln 165 170 Glu Gly Gly Lys Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val 180 185 Cys Asn Gln Ser Leu Gln Gly Ile Ile Ser Trp Gly Gln Asp Pro Cys 195 200 Ala Ile Thr Arg Lys Pro Gly Val Tyr Thr Lys Val Cys Lys Tyr Val

210 215

230

Asp Trp Ile Gln Glu Thr Met Lys Asn Asn

225

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<210> 479 <211> 151

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<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -21..-1
<400> 479
Met Ala Ala Ser Thr Ser Met Val Pro Val Ala Val Thr Ala Ala Val
 -20 -15 -10
Ala Pro Val Leu Ser Ile Asn Ser Asp Phe Ser Asp Leu Arg Glu Ile
   1 5
Lys Lys Gln Leu Leu Leu Ile Ala Gly Leu Thr Arg Glu Arg Gly Leu
            20
Leu His Ser Ser Lys Trp Ser Ala Glu Leu Ala Phe Ser Leu Pro Ala
                         40
         35
Leu Pro Leu Ala Glu Leu Gln Pro Pro Pro Pro Ile Thr Glu Glu Asp
45 50 55
Ala Gln Asp Met Asp Ala Tyr Thr Leu Ala Lys Ala Tyr Phe Asp Val
60 . 65 . 70
Lys Glu Tyr Asp Arg Ala Ala His Phe Leu His Gly Cys Asn Ala Arg
           80 85
Lys Ala Tyr Phe Leu Tyr Met Tyr Ser Arg Tyr Leu Val Arg Ala Ile
      95 100
                              105
Leu Lys Cys His Ser Ala Phe Ser Glu Thr Ser Ile Phe Arg Thr Asn
110 115
Gly Lys Val Lys Ser Phe Lys
  125
<210> 480
<211> 239
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 480
Met Pro Arg Lys Arg Lys Cys Asp Leu Arg Ala Val Arg Val Gly Leu
                    ~15
         -20
Leu Leu Gly Gly Gly Val Tyr Gly Ser Arg Phe Arg Phe Thr Phe
           -5
                        1 5
Pro Gly Cys Arg Ala Leu Ser Pro Trp Arg Val Arg Xaa Gln Arg Arg
           1.5
     1.0
Arg Cys Glu Met Ser Thr Met Phe Ala Asp Thr Leu Leu Ile Val Phe
     30
                               35
Ile Ser Val Cys Thr Ala Leu Leu Ala Glu Gly Ile Thr Trp Val Leu
      45
                             50
Val Tyr Arg Thr Asp Lys Tyr Lys Arg Leu Lys Ala Glu Val Glu Lys
           60
                          65
Gln Ser Lys Lys Leu Glu Lys Lys Lys Glu Thr Ile Thr Glu Ser Ala
            80
                            85
Gly Arg Gin Gln Lys Lys Ile Glu Arg Xaa Xaa Xaa Leu Xaa
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<210> 481 <211> 208 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 481

<222> -92..-1

Met Arg Glu Pro Gln Lys Arg Thr Ala Thr Ile Ala Lys Xaa Xaa Ala -90 -85 -80 Xaa Glu Gly Leu Arg Asp Pro Tyr Gly Arg Leu Cys Gly Ser Glu His -75 -70 -65 Pro Arg Arg Pro Pro Glu Arg Pro Glu Glu Asp Pro Ser Thr Pro Glu -60 -55 -50 -45 Glu Ala Ser Thr Thr Pro Glu Glu Ala Ser Ser Thr Ala Gln Ala Gln -40 -35 -30 Lys Pro Ser Val Pro Arg Ser Asn Phe Gln Gly Thr Lys Lys Ser Leu -25 -20 -15 Leu Met Ser Ile Leu Ala Leu Ile Phe Ile Met Gly Asn Ser Ala Lys -10 -5 1 Glu Ala Leu Val Trp Lys Val Leu Gly Lys Leu Gly Met Gln Pro Gly 10 15 Arg Xaa His Ser Ile Phe Gly Asp Pro Lys Lys Ile Val Thr Glu Xaa 25 30 Phe Val Arg Arg Gly Tyr Leu Ile Tyr Xaa Pro Val Pro Arg Xaa Ser 40 45 50 Pro Val Glu Tyr Xaa Phe Phe Trp Gly Pro Arg Ala His Val Glu Ser 55 60 Ser Xaa Leu Lys Xaa Xaa His Phe Val Ala Arg Val Arg Asn Arg Cys 70 75 Ser Lys Asp Trp Pro Cys Asn Tyr Asp Trp Asp Ser Asp Asp Ala 95 90 95 100 Glu Val Glu Ala Ile Leu Asn Ser Gly Ala Xaa Gly Tyr Ser Ala Pro

105 110

<210> 482

<211> 86

<212> PRT

<213> Homo sapiens

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<221> SIGNAL
<222> -39..-1
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<400> 482

Met Asn Val Gly Thr Ala His Xaa Xaa Val Asn Pro Asn Thr Arg Val -30 -35 Met Asn Ser Arg Gly Ile Trp Leu Ser Tyr Val Leu Ala Ile Gly Leu -15 -20 Leu His Ile Val Leu Leu Ser Ile Pro Phe Val Ser Val Pro Val Val 1 - 5 Trp Thr Leu Thr Asn Leu Ile His Asn Met Gly Met Tyr Ile Phe Leu 20 15 His Thr Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gly Lys Ala

30 Arg Leu Leu Thr His Trp 45

<210> 483 <211> 40 <212> PRT <213> Homo sapiens

<220'> <221> SIGNAL <222> -27..-1

<400> 483

Met Arg Thr Leu Phe Gly Ala Val Arg Ala Pro Phe Ser Ser Leu Thr -25 -20 -15 Leu Leu Leu Ile Thr Pro Ser Pro Ser Pro Leu Leu Phe Asp Arg Gly -5 Leu Ser Leu Arg Ser Ala Met Ser

10

<210> 484 <211> 65 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<400> 484

<222> -16..-1

Met Leu Gly Phe Phe Leu Phe Leu Ser Phe Val Leu Met Tyr Asp Gly -10 - 5 Leu Arg Leu Phe Gly Ile Leu Ser Thr Cys Arg Val His His Thr Met 10 Asn Gln Phe Leu Ile Asp Ile Ser Ser Phe Thr Ser Arg Val Lys 25 30 Lys Ile Phe Leu Phe Tyr Ala Phe Xaa Gly Cys Xaa Phe Gln Ser Ala 40 Thr

<210> 485 <211> 130

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<212> PRT
<213 > Homo sapiens
<220>
<221> SIGNAL
<222> -55..-1
<400> 485
Met Ala Met Trp Asn Arg Pro Xaa Xaa Xaa Leu Pro Gln Gln Pro Leu
                -50
                                       -45
Xaa Ala Glu Pro Thr Ala Glu Gly Glu Pro His Leu Pro Thr Gly Arq
                -35
                                    -30
Xaa Xaa Thr Glu Ala Asn Arg Phe Ala Tyr Ala Ala Leu Cys Gly Ile
                               -15
Ser Leu Ser Gln Leu Phe Pro Glu Pro Glu His Ser Ser Phe Cys Thr
  - 5
Glu Phe Met Ala Gly Leu Val Xaa Trp Leu Glu Leu Ser Glu Ala Val
                   15
Leu Pro Thr Met Thr Ala Phe Ala Ser Gly Leu Gly Gly Glu Gly Xaa
Xaa Cys Val Cys Ser Asn Phe Thr Glu Gly Pro His Leu Glu Gly Arg
                               5.0
Pro Asp Gly Asp His Ser Gly Pro Ser Glu Leu Leu Thr Gln Gly Trp
                          65
Ala Leu
   75
<210> 486
<211> 209
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -84..-1
<400> 486
Met Val Asn Phe Pro Gln Lys Ile Ala Gly Glu Leu Tyr Gly Pro Leu
               -80
                                   -75
Met Leu Val Phe Thr Leu Val Ala Ile Leu Leu His Gly Met Lys Thr
           -65
                               -60
Ser Asp Thr Ile Ile Arg Glu Gly Thr Leu Met Gly Thr Ala Ile Gly
       -50
                           -45
Thr Cys Phe Gly Tyr Trp Leu Gly Val Ser Ser Phe Ile Tyr Phe Leu
                       -30
Ala Tyr Leu Cys Asn Ala Gln Ile Thr Met Leu Gln Met Leu Ala Leu
                   -15
                                       -10
Leu Gly Tyr Gly Leu Phe Gly His Cys Ile Val Leu Phe Ile Thr Tyr
Asn Ile His Leu Arg Ala Leu Phe Tyr Leu Phe Trp Leu Leu Val Gly
                           20
Gly Leu Ser Thr Leu Arg Met Val Ala Val Leu Val Ser Arg Thr Val
                       35
Gly Pro Thr Xaa Arg Xaa Leu Leu Cys Gly Thr Leu Ala Ala Leu His
                   50
                                       55
Met Leu Phe Leu Leu Tyr Leu His Phe Ala Tyr His Lys Xaa Val Xaa
                                   70
Gly Ile Leu Asp Thr Leu Glu Gly Pro Asn Ile Pro Pro Ile Gln Arg
                   85
```

Val Pro Arg Asp Ile Pro Ala Met Leu Pro Ala Ala Arg Leu Pro Thr

```
100
      95
Thr Val Leu Asn Ala Thr Ala Lys Ala Val Ala Val Thr Leu Gln Ser
                              120
110 115
His
125
<210> 487
<211> 36
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -17..-1
<400> 487
Met Gly Trp Gln Arg Trp Trp Cys Phe His Leu Gln Ala Glu Ala Ser
                       -10
                                           - 5
Ala His Pro Pro Gln Gly Leu Gln Ala Gln Phe Ser Cys Cys Pro Trp
                                   10
                5
  1
Val Gly Ile Cys
<210> 488
<211> 44
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -29..-1
Met Met Ser Ser Glu Leu Arg Arg Asn Pro His Phe Leu Lys Ser Asn
              -25
                                 -20
Leu Phe Leu Gln Leu Leu Val Ser His Glu Ile Val Cys Ala Thr Glu
                          - 5
    -10
Thr Val Thr Thr Asn Phe Leu Arg His Glu Lys Ala
                    10
 5
<210> 489
<211> 163
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> ~52..-1
<400> 489
Met Glu His Tyr Arg Lys Ala Gly Ser Val Glu Leu Pro Ala Pro Ser
     -50
                     -45
Pro Met Pro Gln Leu Pro Pro Asp Thr Leu Glu Met Arg Val Arg Asp
 -35
                      -30
                                         -25
Gly Ser Lys Ile Arg Asn Leu Leu Gly Leu Ala Leu Gly Arg Leu Glu
                  -15
                                     -10
Gly Gly Ser Ala Arg His Val Val Phe Ser Gly Ser Gly Arg Ala Ala
```

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```
Gly Lys Ala Val Ser Cys Ala Glu Ile Val Lys Arg Arg Val Pro Gly
                       20
Leu His Gln Leu Thr Lys Leu Xaa Phe Leu Gln Thr Glu Asp Ser Trp
                    35
Val Pro Xaa Ser Pro Asp Thr Gly Leu Xaa Pro Leu Thr Val Arg Arg
                                  55
His Val Pro Ala Xaa Trp Val Leu Leu Xaa Arg Asp Pro Leu Asp Pro
                               70
Asn Glu Cys Gly Tyr Gln Pro Pro Gly Ala Pro Pro Gly Leu Gly Ser
                           85
Met Pro Ser Ser Ser Cys Gly Pro Arg Ser Xaa Lys Arg Ala Xaa Xaa
                       100
Thr Arg Ser
  110
<210> 490
<211> 64
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -47..-1
<400> 490
Met His Gly Phe Glu Ile Ile Ser Leu Lys Glu Glu Ser Pro Leu Gly
  -45 -40 -35
Lys Val Ser Gln Gly Pro Leu Phe Asn Val Thr Ser Gly Ser Ser Ser
          -25
Pro Val Thr Trp Leu Gly Leu Leu Ser Phe Gln Asn Leu His Cys Phe
-15 -10 -5 1
Pro Asp Leu Pro Thr Glu Met Pro Leu Xaa Ala Lys Gly Xaa Asn Thr
                           10
<210> 491
<211> 218
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -50..-1
<400> 491
Met His His Gly Leu Thr Pro Leu Leu Cly Val His Glu Gln Lys
         -45
Gln Gln Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala
             -30
                              -25
Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly
         -15
                           -10
Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser
    1 5
                                     10
Ser Gln Asp Leu Ser Gly Gln Thr Ala Lys Lys Tyr Ala Val Ser Ser
15 20
                                25
Arg His Asn Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Xaa Lys Gln
```

Xaa Leu Lys Val Ser Ser Glu Asn Ser Asn Pro Xaa Gln Asp Leu Lys

<210> 492 <211> 216 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -15..-1 <400> 492 Met Val Cys Val Leu

<400> 492 Met Val Cys Val Leu Val Leu Ala Ala Ala Gly Ala Val Ala Val -15 -10 Phe Leu Ile Leu Arg Ile Trp Val Val Leu Arg Ser Met Asp Val Thr 5 10 Pro Arg Glu Ser Leu Ser Ile Leu Val Val Ala Gly Ser Gly Gly His 20 25 Thr Thr Glu Ile Leu Arg Leu Leu Gly Ser Leu Ser Asn Ala Tyr Ser 45 40 Pro Arg His Tyr Val Ile Ala Asp Thr Asp Glu Met Ser Ala Asn Lys 55 60 65 Ile Asn Ser Phe Glu Leu Xaa Arg Xaa Asp Arg Xaa Pro Ser Asn Met 70 75 Xaa Thr Lys Tyr Tyr Ile His Arg Ile Pro Xaa Ser Arg Glu Val Gln 85 90 95 Gln Ser Trp Pro Ser Thr Val Xaa Thr Thr Leu His Ser Met Trp Leu 100 105 110 Ser Xaa Pro Leu Ile His Arg Val Lys Pro Xaa Leu Val Leu Cys Asn 120 125 Gly Pro Gly Thr Cys Val Pro Ile Cys Val Ser Ala Leu Leu Gly 135 140 145 Ile Leu Gly Ile Lys Lys Val Ile Ile Val Tyr Val Glu Ser Ile Cys 150 155 Arg Val Lys Thr Leu Ser Met Ser Gly Lys Ile Leu Phe His Leu Ser 165 170 175 Asn Tyr Phe Ile Val Gln Trp Pro Ala Leu Lys Glu Lys Tyr Pro Lys 180 185 Ser Val Tyr Leu Gly Arg Ile Val 200

<210> 493
<211> 134
<212> PRT

<213> Homo sapiens <220> <221> SIGNAL <222> -19..-1 <400> 493 Met Pro Leu Gly Ala Arg Ile Leu Phe His Gly Val Phe Tyr Ala Gly -10 - 1.5 Gly Phe Ala Ile Val Tyr Tyr Leu Ile Gln Lys Phe His Ser Arg Thr Leu Tyr Tyr Lys Leu Ala Val Glu Gln Leu Gln Xaa His Pro Glu Ala 20 Gln Glu Ala Leu Gly Pro Pro Leu Asn Ile His Tyr Leu Lys Leu Ile 35 40 Asp Arg Glu Asn Phe Val Asp Ile Val Xaa Ala Lys Leu Lys Ile Pro 55 50 Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr Val His Ser Ser Arg 70 Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu Val Phe Leu Glu Leu 85 Lys Asp Gly Gln Gln Ile Pro Val Phe Lys Leu Ser Gly Glu Asn Gly 100 Asp Glu Val Lys Lys Glu 110 <210> 494 <211> 85 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -16..-1 <400> 494 Met Ala Val Thr Ala Leu Ala Ala Xaa Thr Trp Leu Gly Val Trp Gly -10 -5 Val Arg Thr Met Gln Ala Arg Gly Phe Gly Ser Asp Gln Ser Glu Asn 10 Val Asp Arg Gly Ala Gly Ser Ile Arg Glu Ala Gly Gly Ala Phe Gly 25 2.0 Lys Arg Glu Gln Ala Glu Glu Glu Arg Tyr Phe Arg Ala Gln Ser Thr 40 Glu Gln Leu Ala Xaa Leu Lys Lys Xaa His Glu Glu Glu Ile Val His 55 His Arg Glu Gly Asp

<210> 495 <211> 292 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -29..-1

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<400> 495
Met His Gly Leu Leu His Tyr Leu Phe His Thr Arg Asn His Thr Phe
          -25 -20 -15
Ile Val Leu His Leu Val Leu Gln Gly Met Val Tyr Thr Glu Tyr Thr
                -5
         -10
Trp Glu Val Phe Gly Tyr Cys Gln Glu Leu Glu Leu Ser Leu His Tyr
                1.0
                         15
Leu Leu Pro Tyr Leu Leu Gly Val Asn Leu Phe Phe Thr
             25
                             30 35
Leu Thr Cys Gly Thr Asn Pro Gly Ile Ile Thr Lys Ala Asn Glu Leu
            40
                          4.5
Leu Phe Leu His Val Tyr Glu Phe Asp Glu Xaa Met Phe Pro Lys Asn
                        60
Val Arg Cys Ser Thr Cys Asp Leu Arg Lys Pro Ala Arg Ser Xaa His
          75
Cys Xaa Val Cys Asn Trp Cys Val His Arg Phe Xaa His His Cys Val
      90
Trp Val Asn Asn Cys Ile Gly Ala Trp Asn Ile Arg Xaa Phe Leu Ile
   105
                            110
Tyr Val Leu Thr Leu Thr Ala Ser Ala Ala Thr Val Ala Ile Val Ser
            120
                            125 130
Thr Thr Phe Leu Val His Leu Val Val Met Ser Asp Leu Tyr Gln Glu
                         140 145
Thr Tyr Ile Asp Asp Leu Gly His Leu His Val Met Asp Thr Val Phe
                     155 160
Leu Ile Gln Tyr Leu Phe Leu Thr Phe Pro Arq Ile Val Phe Met Leu
                   170
Gly Phe Val Val Val Leu Xaa Phe Leu Leu Gly Gly Tyr Leu Leu Phe
180 185 190
Val Leu Tyr Leu Ala Ala Thr Asn Gln Thr Thr Asn Glu Trp Tyr Arg
            200 205 210
Xaa Asp Trp Ala Trp Cys Gln Arg Cys Pro Leu Val Ala Trp Pro Pro
         215
             220 225
Ser Ala Glu Pro Gln Val His Arg Asn Ile His Ser His Gly Leu Arg
      230 235 240
Xaa Asn Leu Gln Glu Ile Phe Leu Pro Ala Phe Pro Cys His Glu Arg
                  250
Lys Lys Gln Glu
260
```

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<210> 496
<211> 122
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -56..-1
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<400> 496

Met Thr Gly Phe Leu Leu Pro Pro Ala Ser Arg Gly Thr Arg Arg Ser -50 -45 Cys Ser Arg Ser Arg Lys Arg Gln Thr Arg Arg Arg Asn Pro Ser -40 -35 -30 -25 Ser Phe Val Ala Ser Cys Pro Thr Leu Leu Pro Phe Ala Cys Val Pro -20 -15 -10 Gly Ala Ser Pro Thr Thr Leu Ala Phe Pro Pro Val Xaa Leu Thr Gly 1 - 5 Pro Xaa Thr Asp Gly Ile Pro Phe Ala Leu Xaa Ser Ala Ala Gly Pro 10 15

WO 99/31236 -349- PCT/IB98/02122 -

 Phe
 Cys
 Ala
 Ser
 Phe
 Pro
 Ser
 Gly
 Xaa
 Leu
 Ser
 Pro
 Pro
 Leu
 Ala
 Leu
 Pro
 Ser
 Val
 Phe
 Tyr
 Ser
 Cys
 Gly

 Ala
 His
 Pro
 Lys
 Val
 Leu
 Lys
 Val
 Leu
 L

<210> 498 <211> 99 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -13..-1

Arg Gln Leu 85

<210> 499 <211> 99 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -13..-1
<400> 499
Met His Leu Leu Ser Asn Trp Ala Asn Pro Ala Ser Ser Arg Arg Pro
           -10
                - 5
Ser Met Ala Ala Ser Gly Thr Ser Trp Ile Ser Ser Thr Leu Ala His
                                      15
                      10
Ser Leu Ser Leu Arg Asp Val Ser Glu Arg Leu Cys Ser Cys Trp Arg
                  25
                                     30
Thr Ile Ser Met Gly Pro Cys Ala Arg Gly Ser Pro Met Asn Ser Ser
              40
                          4.5
Gly Val His Arg Lys Ser Ser Arg Leu Phe Tyr Ile Arg Thr Pro Met
Arg Arg Ser Ser Cys His Leu Xaa Cys Gln Val Ile Phe Leu Leu Gly
                         75
Arg Gln Leu
   85
<210> 500
<211> 108
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -25..-1
<400> 500
Met Ser Leu Thr Ser Ser Ser Ser Val Arg Val Glu Trp Ile Ala Ala
-25 -20
                                     -15
Val Thr Ile Ala Ala Gly Thr Ala Ala Ile Gly Tyr Leu Ala Tyr Lys
              -5
                               1
Arg Phe Tyr Val Lys Asp His Arg Asn Lys Ala Met Ile Asn Leu His
      10
                15
Ile Gln Lys Asp Asn Pro Lys Ile Val His Ala Phe Asp Met Glu Asp
                              35
           30
Leu Gly Asp Lys Ala Val Tyr Cys Arg Cys Trp Arg Ser Lys Lys Phe
                45
                                   50
Pro Phe Cys Asp Gly Ala His Thr Lys His Asn Glu Glu Thr Gly Asp
             60
                             65
Asn Val Gly Pro Leu Ile Ile Lys Lys Lys Glu Thr
           75
                             80
<210> 501
<211> 183
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -15..-1
<400> 501
Met Glu Ala Met Trp Leu Leu Cys Val Ala Leu Ala Val Leu Ala Trp
                      <del>-</del> 5
                  -10
```

Gly Phe Leu Trp Val Trp Asp Ser Ser Glu Arg Met Lys Ser Arg Glu

```
10
Gln Gly Arg Arg Leu Gly Ala Glu Ser Arg Thr Leu Leu Val Ile Ala
                       2.5
His Pro Asp Asp Glu Ala Met Phe Phe Ala Pro Thr Val Leu Gly Leu
                    40
                                     45
Ala Arg Leu Arg His Trp Val Tyr Leu Leu Cys Phe Ser Ala Gly Asn
                55
                                 60
Tyr Tyr Asn Gln Gly Glu Thr Arg Lys Lys Glu Leu Leu Gln Ser Cys
             70
                              75
Asp Val Leu Gly Ile Pro Leu Ser Ser Val Met Ile Ile Asp Asn Arg
                          90
Asp Phe Pro Xaa Asp Pro Gly Met Gln Trp Asp Thr Xaa His Val Ala
     100 105
Xaa Val Leu Leu Gln His Ile Glu Val Asn Gly Ile Asn Leu Val Val
         120
Thr Phe Asp Ala Gly Gly Xaa Ser Gly His Ser Asn His Ile Ala Leu
       135 140 145
Tyr Ala Ala Val Arg Lys Leu Glu Gly Gln Ile Cys Lys Pro Cys Gly
            150
                       155
Thr Gly Gln Asp Phe Lys Glu
```

<210> 502 <211> 98 <212> PRT <213> Homo sapiens <220> <221> SIGNAL

<222> ~15..-1

<210> 503 <211> 183 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -57..-1

Met Leu Lys Lys Tyr Ser His His Arg Asn Ile Ala Thr Tyr Tyr Gly -35 Ala Phe Ile Lys Lys Asn Pro Pro Gly Met Asp Asp Gln Leu Trp Leu -15 -20 Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr Asp Leu Ile Lys Asn -5 1 5 Thr Lys Gly Asn Thr Leu Lys Glu Glu Trp Ile Ala Tyr Ile Cys Xaa 10 15 Glu Ile Leu Arg Gly Leu Xaa His Leu His Gln His Lys Val Ile His 30 35 Arg Xaa Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala Glu Val 45 50 Lys Leu Val Asp Phe Gly Xaa Xaa Ala Gln Leu Asp Arg Thr Val Gly 65 Arg Xaa Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Xaa Val 80 Ile Ala Cys Asp Glu Asn Pro Xaa Ala Thr Tyr Asp Phe Lys Xaa Asp 90 95 Leu Trp Ser Leu Gly Ile Thr Ala Ile Glu Met Ala Glu Gly Leu Pro 110 Leu Ser Val Thr Cys Thr Pro 125

<210> 504 <211> 140 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -14..-1 <400> 504 Met Phe Leu Thr Ala Leu Leu Trp Arg Gly Arg Ile Pro Gly Arg Gln -10 -5 Trp Ile Gly Lys His Arg Arg Pro Arg Phe Val Ser Leu Arg Ala Lys 10 Gln Asn Met Ile Arg Arg Leu Glu Ile Glu Ala Glu Asn His Tyr Trp 25 Leu Ser Met Pro Tyr Met Thr Arg Glu Glu Glu Arg Gly His Ala Ala 4 0 45 Leu Arg Arg Arg Glu Ala Phe Glu Ala Ile Lys Ala Ala Ala Thr Ser 5.5 Lys Phe Pro Pro His Arg Phe Ile Ala Asp Gln Leu Asp His Leu Asn 75 Xaa His Gln Glu Met Val Leu Ile Leu Ser Arg His Pro Trp Ile Leu 90 Trp Ile Thr Glu Leu Thr Ile Phe Thr Trp Ser Gly Leu Lys Asn Cys 100 105 110 Ser Leu Cys Glu Asn Glu Leu Trp Thr Ser Leu Tyr 120

<210> 505 <211> 59 <212> PRT

<213> Homo sapiens

<220>

<221> SIGNAL <222> -14..-1 <400> 505 Met Ala Ala Leu Val Thr Val Leu Phe Thr Gly Val Arg Arg Leu His -10 -5 Cys Ser Ala Xaa Leu Gly Arg Ala Ala Ser Gly Xaa Tyr Ser Arg Asn 5 10 15 Trp Leu Pro Thr Pro Pro Ala Thr Gly Pro Leu Pro Ser Ser Gln Thr 20 25 30 Gly His Met Arg Met Ala Ala Leu Leu Pro Gln 35 40 45 <210> 506 <211> 101 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -36..-1 <400> 506 Met Gly Pro Tyr Asn Val Ala Val Pro Ser Asp Val Ser His Ala Arg -35 -30 -25 Phe Tyr Phe Leu Phe His Arg Pro Leu Arg Leu Leu Asn Leu Leu Ile -20 -15 -10 · -5 Leu Ile Glu Gly Ser Val Val Phe Tyr Gln Leu Tyr Ser Leu Leu Arg 1 5 10 Ser Glu Lys Trp Asn His Thr Leu Ser Met Ala Leu Ile Leu Phe Cys 15 20 25 Asn Tyr Tyr Val Leu Phe Lys Leu Leu Arg Asp Arg Xaa Xaa Leu Gly 30 35 40 Arg Ala Tyr Ser Tyr Pro Leu Asn Ser Tyr Glu Leu Lys Ala Asn Xaa 45, 50 Ala Ala Ser Xaa Gln 65 <210> 507 <211> 341 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -55..-1 <400> 507 Met Arg Lys Val Val Leu Ile Thr Gly Ala Ser Ser Gly Ile Gly Leu -55 -50 -45 Ala Leu Cys Lys Arg Leu Leu Ala Glu Asp Asp Glu Leu His Leu Cys -35 -30 Leu Ala Cys Arg Asn Met Ser Lys Ala Glu Ala Val Cys Ala Ala Leu -20 -15 -10 Leu Ala Ser His Pro Thr Ala Glu Val Thr Ile Val Gln Val Asp Val

-5 1 5

10 15

Ser A**sn** Leu Gln Ser Phe Phe Arg Ala Ser Lys Glu Leu Lys Gln Arg

```
Phe Gln Arg Leu Asp Cys Ile Tyr Leu Asn Ala Gly Ile Met Pro Asn
                                 3.5
Pro Gln Leu Asn Ile Lys Ala Leu Phe Phe Gly Leu Phe Ser Arg Lys
           4.5
                             50
Val Ile His Met Phe Ser Thr Ala Glu Gly Leu Leu Thr Gln Gly Asp
                         65
Lys Ile Thr Ala Asp Gly Leu Gln Glu Val Phe Glu Thr Asn Val Phe
                     8.0
                              85
Gly His Phe Ile Leu Ile Arg Glu Leu Glu Pro Leu Leu Cys His Ser
                95
                                   100
Asp Asn Pro Ser Gln Leu Ile Trp Thr Ser Ser Arg Ser Ala Arg Lys
              110
                                115 120
Ser Asn Phe Ser Leu Glu Asp Phe Gln His Ser Lys Gly Lys Glu Pro
                             130
Tyr Ser Ser Ser Lys Tyr Ala Thr Asp Leu Leu Ser Val Ala Leu Asn
                                 150
                         145
Arg Asn Phe Asn Gln Gln Gly Leu Tyr Ser Asn Val Ala Cys Pro Gly
                     160
                                       165
Thr Ala Leu Thr Asn Leu Thr Tyr Gly Ile Leu Pro Pro Phe Ile Trp
                  175
                                    180
Thr Leu Leu Met Pro Ala Ile Leu Leu Leu Arg Phe Phe Ala Asn Ala
                                195
Phe Thr Leu Thr Pro Tyr Asn Gly Thr Glu Ala Leu Val Trp Leu Phe
          205
                             210
His Gln Lys Pro Glu Ser Leu Asn Pro Leu Ile Lys Tyr Leu Ser Ala
      220
                         225
                                          230
Thr Thr Gly Phe Gly Arg Asn Tyr Ile Met Thr Gln Lys Met Asp Leu
                     240
                                       245
Asp Glu Asp Thr Ala Glu Lys Phe Tyr Gln Lys Leu Leu Glu Leu Glu
                  255
                                  260
Lys His Ile Arg Val Thr Ile Gln Lys Thr Asp Asn Gln Ala Arg Leu
              270
                          275
Ser Gly Ser Cys Leu
          285
```

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<210> 508
<211> 108
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -42..-1
<400> 508
Met His Ile Leu Gln Leu Leu Thr Thr Val Asp Asp Gly Ile Gln Ala
                          -35
                                     -30
Ile Val His Cys Pro Asp Thr Gly Lys Asp Ile Trp Asn Leu Leu Phe
                      -20
Asp Leu Val Cys His Glu Phe Cys Gln Ser Asp Asp Pro Ala Ile Ile
-10 -5
                                    1 5
Leu Gln Xaa Gln Lys Thr Val Leu Ala Ser Val Phe Ser Val Leu Ser
          10
Ala Ile Tyr Ala Ser Gln Thr Glu Gln Xaa Tyr Leu Lys Ile Xaa Lys
Gly Asp Gly Gly Ser Gly Ser Lys Gly Arg Pro Xaa Xaa Gln Thr Glu
                      45
Xaa Phe Leu Cys Ile Ser Lys Pro Ser Ser Phe Leu
```

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<210> 509
<211> 80
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -26..-1
<400> 509
Met Glu Glu Ile Ser Ser Pro Leu Val Glu Phe Val Lys Val Leu Cys
 -25 -20
                                 -15
Thr Asn Gln Val Leu Ile Thr Ala Arg Ala Val Pro Thr Lys Lys Ala
-10 -5
Ser Val Arg Cys Val Glu Lys Arg Phe Trp Ile Pro Lys Thr Thr Ser
  10
                          15
Lys His Leu Ser Arg Cys Ile Asp Gly Ile Ser Gly Phe Leu Asn Asp
                         30
Phe Thr Phe Cys Leu Glu Phe Ser Arg His Arg Cys Gln Leu Thr Glu
<210> 510
<211> 158
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
<222> -44..-1
<400> 510
Met Ala Gly Phe Leu Asp Asn Phe Arg Trp Pro Glu Cys Glu Cys Ile
                                 -35
               -40
Asp Trp Ser Glu Arg Arg Asn Ala Val Ala Ser Val Val Ala Gly Ile
                                                -15
                             -20
           -25
Leu Phe Phe Thr Gly Trp Trp Ile Met Ile Asp Ala Ala Val Val Tyr
                       - 5
Pro Lys Pro Glu Gln Leu Asn His Ala Phe His Thr Cys Gly Val Phe
                 10
                                  15
Ser Thr Leu Ala Phe Phe Met Ile Asn Ala Val Ser Asn Ala Gln Val
                                30
              2.5
Arg Gly Asp Ser Tyr Glu Ser Gly Cys Leu Gly Arg Thr Gly Ala Arg
Val Trp Leu Phe Ile Gly Phe Met Leu Met Phe Gly Ser Leu Ile Ala
                          60
Ser Met Trp Ile Leu Phe Gly Ala Tyr Val Thr Gln Asn Thr Asp Val
                      75
                                      80
Tyr Pro Gly Leu Ala Val Phe Phe Gln Asn Ala Leu Ile Phe Phe Ser
                              95
           90
```

Thr Leu Ile Tyr Lys Phe Gly Arg Thr Glu Glu Leu Trp Thr

<210> 511 <211> 130 <212> PRT <213> Homo sapiens

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<220>
<221> SIGNAL
<222> -28..-1
<400> 511
Met Asn Trp Glu Leu Leu Trp Leu Leu Val Leu Cys Ala Leu Leu
         ~25 -20
Leu Leu Leu Val Gln Leu Leu Arg Phe Leu Arg Ala Asp Gly Asp Leu
              ~5
Thr Leu Leu Trp Ala Glu Trp Gln Gly Arg Arg Pro Glu Trp Glu Leu
              10
                         15
Thr Asp Met Val Val Trp Val Thr Gly Ala Ser Ser Gly Ile Gly Glu
                     30
Glu Leu Ala Tyr Gln Leu Ser Lys Leu Gly Val Ser Leu Val Leu Ser
          40
                          4.5
Ala Arg Arg Val His Glu Leu Glu Arg Val Lys Arg Arg Cys Leu Glu
                       60
Asn Gly Asn Leu Lys Glu Lys Asp Ile Leu Val Leu Pro Leu Asp Leu
 70 75
                            80
Thr Asp Thr Gly Ser His Glu Ser Gly Tyr Gln Ser Cys Ser Pro Gly
              90
Ile Trp
```

<210> 512 <211> 199 <212> PRT <213> Homo sapiens <220> <221> SIGNAL <222> -62..-1 <400> 512 Met Ser Gln Arg Ser Leu Cys Met Asp Thr Ser Leu Asp Val Tyr Arg ~55 Xaa Leu Ile Glu Leu Asn Tyr Leu Gly Thr Val Ser Leu Thr Lys Cys -40 -35 Val Leu Pro His Met Ile Glu Arg Lys Gln Gly Lys Ile Val Thr Val -25 -20 Asn Ser Ile Leu Gly Ile Ile Ser Val Pro Leu Ser Ile Gly Tyr Cys -10 -5 1 Ala Ser Lys His Ala Leu Arg Gly Phe Phe Asn Gly Leu Arg Thr Glu 5 10 Leu Ala Thr Tyr Pro Gly Ile Ile Val Ser Asn Ile Cys Pro Gly Pro 20 25 30 Val Gln Ser Asn Ile Val Glu Asn Ser Leu Ala Gly Glu Val Thr Lys 40 45 Thr Ile Gly Asn Asn Gly Asn Gln Ser His Lys Met Thr Thr Ser Arg 55 60 65 Cys Val Arg Leu Met Leu Ile Ser Met Ala Asn Asp Leu Lys Glu Val 75 Trp Ile Ser Glu Gln Pro Phe Leu Leu Val Thr Tyr Leu Trp Gln Tyr 90 Met Pro Thr Trp Ala Trp Trp Ile Thr Asn Lys Met Gly Lys Lys Arg 105 110 Ile Glu Asn Phe Lys Ser Gly Val Asp Ala Xaa Ser Ser Tyr Phe Lys 125 130 120 Ile Phe Lys Thr Lys His Asp

```
<210> 513
<211> 180
<212> PRT
<213> Homo sapiens
<220>
<221> SIGNAL
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